INTRODUCTION

As the world population expands, and as life expectancy increases, the number of elderly rises as well. The ageing of the population is irreversible, and has profound medical consequences ***(Owens et al., 2011).*** One of such consequences is Diabetes Mellitus (DM), the prevalence of DM has increased significantly worldwide and there is a rapid increase in numbers of elderly diabetics ***(Sloan et al., 2008).***

Globally, an estimated 422 million adults are living with DM ***(WHO, 2016).*** This number is expected to double by 2030. Type 2 diabetes (T2D) represents 85-90% of all cases. The increase in the overall diabetes prevalence is believed to be due to increase in risk factors for type 2 as well as greater longevity and obesity ***(WHO, 2016).***

In DM, protein, lipid and nucleic acid alteration is involved, as well as cross-linking and formation of non-degradable aggregates, such as advanced glycation end products (AGEs). Formation of endogenous or uptake of dietary AGEs can lead to further protein modifications and initiation of several inflammatory signaling pathways ***(Ott et al., 2014).***

Aggravated by the fact that endogenous repair and degradation systems become impaired during the aging process, damaged and dysfunctional proteins can accumulate and lead to neurodegenerative and vascular diseases ***(Wei et al., 2013).***

In the context of cardiovascular disease, AGEs can induce cross linking of collagen, leading to vascular stiffening and entrapment of low-density lipoprotein particles (LDL) in the artery walls. AGEs can also cause glycation of LDL which can promote its oxidation ***(Prasad et al., 2012).*** Oxidized LDL is the major factor in the development of atherosclerosis ***(Di Marco et al., 2013).***

Evidence also suggests that AGEs contribute to cognitive impairment by increasing the formation and deposition of neurofibrillary tangles and amyloid plaques, the hallmarks of Alzheimer's disease (AD) ***(Yaffe et al., 2011).***

Despite having the highest prevalence of diabetes, elderly have often been excluded from studies of DM complications especially in Egypt.

This research aims to detect the relationship between advanced glycation end products, coronary risk factors, and cognitive and executive function in elderly diabetics.

Aim of the Study

The aim of this study is to detect the relationship between advanced glycation end products and coronary risk factors and cognitive and executive function in elderly diabetics.

Overview of Diabetes Mellitus

As defined by American diabetes association DM is diagnosed when Fasting Blood Sugar (FBS) ≥ 126 mg/dl or 2hours post prandial (2 hrs PP) ≥200 mg/dl or Hemoglobin A1C (HbA1C) ≥6.5 on repeated testing. When patient has symptoms of hyperglycemia one random blood sugar reading ≥200 mg/dl is considered diagnostic ***(ADA, 2018).***

The International Diabetes Federation (IDF) listed Egypt among the world top 10 countries in diabetes prevalence. The prevalence of diabetes is estimated 15.56% among adults between 20 and 79 years of age, with an annual death of 86,478 related to diabetes.

In 2013, the IDF estimated that 7.5 million Egyptians suffered from diabetes and 2.2 million from prediabetes. Furthermore, reports indicated that 43% of diabetics and prediabetics in Egypt were undiagnosed ***(IDF, 2013).***

In fact, worldwide, DM is considered a major health problem. DM complications and co-morbidities are more frequent in elderly diabetics compared to their young counterparts ***(Chentli et al., 2015).***

DM is the sixth most common cause of death among elderly. However, its role in mortality in the aging population is understated, because in cases of cardiovascular cause of death, diabetes is often not listed as a contributing cause ***(Meneilly and Tessier, 2001).***

Elderly patients have a disproportionately higher prevalence of endocrine and metabolic dysfunction leading to unique patterns of morbidity and making treatment more challenging ***(Sinclair, 2010)***.

Complications and management of DM in elderly vary according to disease duration, environmental factors, and co-morbidities. Some elderly do not suffer from complications and their management is simple; while others are more complicated and have additional diseases difficult to manage even in tertiary centers. Complicated cases are among survivors of early onset DM ***(Chentli et al., 2015).*** The main troublesome co-morbidities in elderly are cardiac and renal insufficiencies leading to limitation in drug prescription ***(Chentli et al., 2015).***

In addition to the classic macrovascular and microvascular diseases, geriatric syndromes as functional impairment, falls, fractures and sensory impairment occur at higher frequency in older adults with diabetes and may affect self-care abilities and health outcomes including quality of life ***(Laiteerapong et al., 2012).***

Risk factors for DM in elderly:

T2D in elderly results from several factors as genetic background and longer life expectancy leading to decrease in insulin secretion, and to the modification of some environmental factors responsible for central obesity ***(Tyrovolas et al., 2015).***

The increase in DM prevalence parallels that of obesity. Some experts call this dual epidemic '*diabesity*'. One consequence of elevated body mass index (BMI) and waist circumference is an increased risk of developing T2D ***(Subhashini, 2011).***

In a recent survey in Egypt, it was found that lack of physical activity is a risk factor for chronic diseases as diabetes mellitus, hypertension, and dyslipidemia. The survey concluded that the majority of these patients did not engage in any form of physical activity even as regular walking ***(Ghandour, 2015).***

Hepatitis C was identified to contribute to diabetes mellitus. The prevalence of T2D among patients with HCV is 13%-33%. A meta-analysis of the association of HCV and T2D concluded that patients with HCV are more prone to develop T2D. The odds ratio was particularly high among male patients and those older than 40 years of age ***(Elharawi et al., 2011).*** Not only does HCV increase T2D risk but it also worsens its control and is associated with increased prevalence of diabetes complications ***(Hegazi et al., 2015).***

Some recent studies as well have also demonstrated the role of other factors such as arginine vasopressin (AVP) or its c-terminal fragment, called Copeptin, in the mechanism of DM in older people by lowering insulin sensitivity ***(Wannamethee et al., 2015).*** AVP affects liver glycogenolysis and glucagon secretion as well ***(Enhörning et al., 2011).***

Moreover, in elderly, some studies concluded that Vitamin D is a potent immunomodulator linked to many major human diseases including glucose homeostasis and insulin resistance. Vitamin D deficiency has been shown to affect insulin secretion in both humans and animal models. Accumulating evidence suggests the role of vitamin D in the pathogenesis of insulin resistance and stated that supplementations of vitamin D may provide suitable management and act to ameliorate insulin resistance ***(Sung et al., 2012).***

Complications of DM

Diabetes Mellitus is associated with a large number of complications with acute complications as diabetic ketoacidosis and/or hypoglycemia and chronic complications ***(Forbes and Cooper, 2013).***

Chronic complications are due to chronic elevation of blood glucose, and are grouped under: "microvascular disease" due to small blood vessels injury, and "macrovascular disease "due to arterial damage ***(Forbes and Cooper, 2013).***

The risk of macrovascular events (cardiovascular disease, cerebrovascular disease, and peripheral vascular disease) is doubled in diabetic seniors in comparison to controls ***(Meneilly and Tessier, 2001)***. Studies concluded that DM carries a twofold increased risk for ischemic heart disease independent from other established risk factors ***(Sarwar et al., 2010)***.

The risk of macrovascular events is related to duration and control of diabetes; as well as the well-known risk factors as smoking, hypertension and, elevated cholesterol level ***(Meneilly and Tessier, 2001)***.

The risk of microvascular complications (nephropathy, retinopathy and neuropathy) also increases with advanced age. And, again, there is an important correlation between these micro vascular complications and values of glycated hemoglobin, duration of diabetes, high blood pressure, and hyperlipidemia ***(Meneilly and Tessier, 2001)***.

Depression, dementia, and sexual dysfunction are among other diabetes complications ***(Nouwen et al., 2011); (Cukierman et al., 2005).***

Older adults with diabetes have higher rates of major lower-extremity amputation**,** myocardial infarction (MI), visual impairment, and end-stage renal disease than any other age-group ***(Li et al., 2012***). Those aged ≥75 years in particular, have higher rates than younger patients for most complications ***(CDC, 2012)***.

Mortality from hyperglycemic crises is also higher in elderly patients. Moreover, those aged ≥75 years have two fold higher rate of emergency department visits for hypoglycemia than younger diabetics ***(CDC, 2012)***.

The care of elderly diabetics is far more complicated than younger adults as they have a higher risk of geriatric syndromes, drug-related hypoglycemia, and diabetes complications ***(Brown et al., 2003).***

Pathophysiology of DM Complications

Diabetes induces pathognomonic changes in capillaries basement membrane including arterioles in the nephrons, retina, cardiac muscle, skin, and muscle, through increasing their thickness, leading to diabetic microangiopathy ***(Chawla et al., 2016)***. This micro-angiopathy leads to abnormalities in blood vessels function, manifesting clinically as elevated blood pressure, impaired wound healing, and tissue hypoxia. Also, neovascularization arising from the vasa vasorum may interconnect macro-and microangiopathy, predicts platelet rupture and induces atherosclerosis ***(Chawla et al., 2016).***

Common Pathophysiological mechanisms of DM Complications:

1- Production of Advanced Glycation end products:

AGEs are a heterogeneous group of molecules, resulting from nonenzymatic glycation of plasma proteins (chapter 2).

This process leads to abnormal function of plasma proteins due to changes in their molecular structure, resulting in alteration in enzymatic activity and receptor function. AGEs accumulate in cells as well and affect their function through cross-linking. This cross linking is not only with proteins but also lipids and nucleic acids contributing to many diabetic complications ***(Singh et al., 2014).***

Additionally, AGEs affect LDL particles structure and together with vascular damage enhances atherosclerosis ***(Goldin et al., 2006)*.**

2- Increased oxidative stress:

Hyperglycemia increases production of Reactive Oxygen Species (ROS). ROS leads to oxidative stress, which initiates other pathological pathways responsible for many diabetic complications as activating polyol pathway, Protein Kinase C (PKC) and nonenzymatic glycation. All of these pathways are responsible for micro and macro vascular complications ***(Jakus and Rietbrock 2004).*** ROS also block two anti-atherosclerotic enzymes: prostacyclin synthatase and endothelial nitric oxide synthetase ***(Folli et al., 2011).***

ROS interacts with cellular proteins and DNA leading to excessive cellular damage. Most commonly affected organelle is mitochondrial DNA. ROS leads to early mitochondrial DNA damage in human retinal endothelium ***(Giacco and Brownlee 2010)***.

It is important to notice that cellular damage mediated by ROS leads to what is known as pathological "memory" in small blood vessels which persists for longtime after glucose level normalization.

Many studies concluded that superoxide production is the principal cause of metabolic abnormalities in diabetes ***(Xie et al., 2008)***.

Insulin Resistance (IR) leads to mitochondrial ROS production from free fatty acids and inhibits anti-atherosclerotic enzymes causing atherosclerosis and cardiomyopathy in patients with T2D. In individuals with higher levels of insulin resistance there is a two fold increase in cardiovascular disease risk compared to individuals with less insulin resistance. This risk is calculated after adjusting other risk factors as lipid profile, smoking and systolic blood pressure ***(Duncan, 2011).***

3- Low-grade inflammation:

Inflammation is an important risk factor in both atherosclerosis and T2D. Hyperglycemia leads to pathological changes in vascular cells, leading to adhesion of monocyte to endothelial Cells, which is an early step in atherogenesis ***(Syed et al., 2013).***

Inflammatory markers as C-reactive protein, fibrinogen, plasminogen activator inhibitor I, and interleukine-6 levels increase with the onset of diabetes. Also, monocyte activation with hyperglycemia leads to induction of inflammatory mediators such as PKC and nuclear factor-κB leading to oxidative stress ***(Otsuka et al., 2005).*** Additionally, the role of increased level of tumor necrosis factor alpha in the development of IR is well-documented ***(Otsuka et al., 2005*)**.

4- Neovascularization of vasa vasorum:

The proliferation of vasa vasorum leads to increased plaque burden, which increases atherosclerosis process ***(Tian et al., 2013).***

Inflammation, plaque perfusion and intra-plaque hemorrhage are critical during the development of atherosclerotic plaques and are related to vasa vasorum neovascularization. Neovascularization develops by the growth from both adventitial layer and arterial lumen toward the intima ***(Hayden and Tyagi, 2004).***

In T2D, plaque rupture is associated with increased angiogenesis, and diabetic atherosclerosis is further accelerated by neovasculature microangiopathy **(*Patel, 2014).*** The initial angiogenic response in the adventitial vasa vasorum, is triggered by hypoxia through identification of increased hypoxia-inducible factor and vascular endothelial growth factor (VEGF) action. ***(Xu et al., 2015)*** VEGF, is a cytokine that contributes to microvascular complications by increasing the vascular permeability to macromolecules, monocyte chemotaxis, and tissue factor production ***(Bonnefond et al., 2013).*** However, VEGF treatment has been shown to restore microcirculation in the vasa nervorum and decrease diabetic neuropathy in experiments **(*Orasanu and Plutzky, 2009).***

In the eye, a neurotropic factor-pigment epithelium-derived factor (PEDF) may inhibit VEGF action by its potent angiogenic inhibition ***(Schratzberger et al., 2001).*** PEDF level is decreased in proliferative diabetic

retinopathy, but VEGF levels are increased. Decreased PEDF levels may also promote diabetic nephropathy. Other growth factors such as insulin-like growth factor 1, basic fibroblast growth factor, and hepatocyte growth factor may lead to proliferative retinopathy ***(Gao et al., 2001)***.

Pathophysiology of Advanced glycation end products

Production of AGEs

Maillard Reaction

It is the non-enzymatic reaction between the free amino groups and carbonyl groups of reducing sugars or other carbonyl compounds ***(Helou et al., 2014)***. This reaction is subdivided into three main steps: early, intermediate, and late (Fig. 1).

In the early step, glucose (or other reducing sugars such as fructose, mannose, xylulose, galactose, pentoses) reacts with a free amino group of biological amines producing an unstable compound called the Schiff base. The Shiff Base is then transformed to a more stable complex named the Amadori product ***(Monnier et al., 1996).***

In the intermediate stage, the amadori product degrades to one of many reactive dicarbonyl compounds such as deoxyglucosones, glyoxal and methyl glycoxal (MGO) through dehydration, oxidation and other chemical reactions. In the late stage of glycation, irreversible compounds "the AGEs" are produced through dehydration, oxidation and cyclization reactions ***(Monnier et al., 1996).***

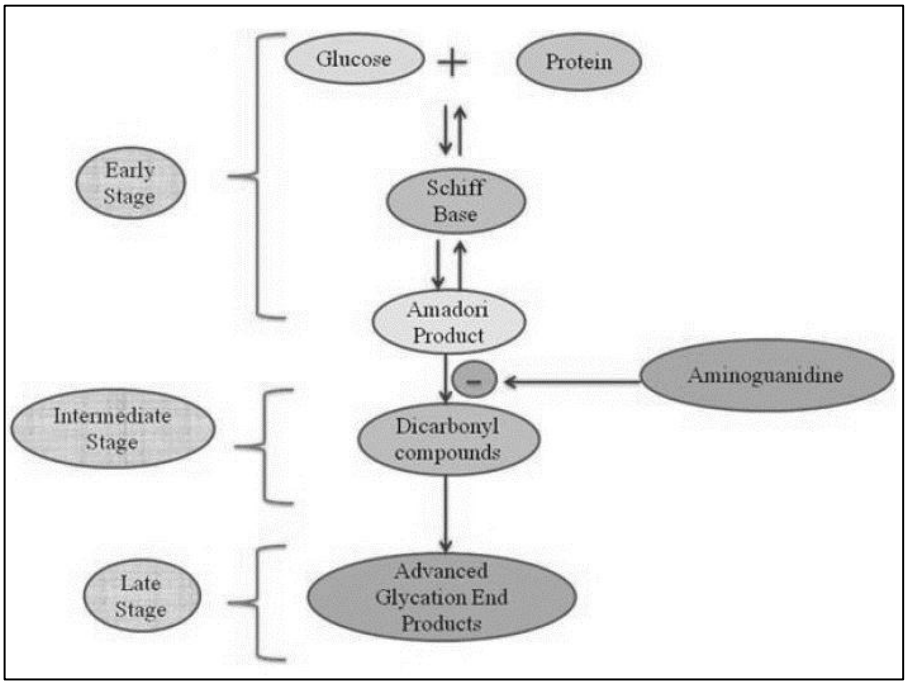

Fig. (1): Maillard reaction ***(Singh et al., 2014).***

Another proven pathway of AGEs in absence of diabetes, is through nutrients processed by common methods such as dry heat ***(Koschinsky et al., 1997)*** or during tobacco smoking ***(Cerami et al., 1997).***

Food processing, through dry heat, ionization or irradiation, significantly increases the production of new AGEs ***(Obrien et al., 1989; Cai et al., 2002).***

Simple home cooking methods through heat and dehydration increase the production of AGEs. In food industry AGEs improves flavor and are highly required to increase food consumption ***(Van Boeket, 2006).***