The relationship between advanced glycation end products and coronary risk factors and abdominal aortic diameter and peripheral arterial disease in elderly diabetics

Thesis

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Contents

Subjects	Page

- List of Abbreviations I
- List of table II
- List of Figures III
- Introduction 1
- Aim of the Work 4
- Review of literature: .....

Chapter 1: Definition and description of Diabetes Mellitus 5

Chapter 2: DM and Cardiovascular Diseases 16

Chapter 3: DM and Peripheral Arterial Disease (PAD) 20

Chapter 4: DM and Abdominal Aortic Aneurysm (AAA) 24

Chapter 5: Potential therapeutic opportunities targeting AGE-related processes 30

- Patients And Methods 34
- Results 42
- Discussion 50
- Summary 64
- Conclusion 67
- Recommendations 68
- References 69
- Arabic Summary ..... -

List of Abbreviations

AAA	: Abdominal aortic aneurysm
ABI	: Ankle brachial index
AGER1	: Advanced glycated end-product receptor 1
AGEs	: Advanced glycation end products
CAD	: Coronary artery disease
CML	: Carboxymethyllysine
CQAs	: Caffeoylquinic acids
CVD	: Cardiovascular disease
DM	: Diabetes mellitus
ECM	: Extra cellular matrix
EF	: Ejection fraction
ELISA	: Enzyme-linked immunosorbent assays
HDL	: High density lipoproteins
HPLC	: High-performance liquid chromatography
HRP	: Horseradish peroxidase
HRQoL	: Health related quality of life
hs-CRP	: High sensitivity c reactive protein
IADL	: Instrumental activities of daily living
ILK	: Integrin-linked kinase
LDL	: Low density lipoproteins
MAPK	: Mitogen-activated protein kinase
MG	: Methylglyoxal
MS	: Mass spectrometry
MTOR	: Mammalian target of rapamycin
NF-κB	: Nuclear factor kappa-b
OS	Oxidative stress
PAD	Peripheral arterila disease
PKC	Protein kinase c
RAAS	Renin-angiotensin-aldosterone system
RAGE	Receptors of advanced glycation end-products
ROS	Reactive oxygen species
SMC	Smooth muscle cells
TG	Triglycerides
VEGF	Vascular endothelial growth factor
VSMC	Vascular smooth muscle cell
WHO	World health organization

List of Table

Tab. No.	Subject	Page
Table (1)	Comparison between study groups regarding the demographic data:	42
Table (2)	Comparison between study groups regarding laboratory result	43
Table (3)	(a and b): Description of cardiovascular diseases among group 3	44
Table (4)	(a and b): Comparison between study groups regarding Abdominal Aortic Diameter AAD)	45
Table (5)	(a and b): Comparison between study groups regarding Ankle brachial index (ABI)	46
Table (6)	Comparison between study groups regarding coronary risk [measured using the ASCVD (atherosclerotic cardiovascular disease) algorithm]	47
Table (7)	Description of Advanced Glycation End-products (AGEs) among study groups	48
Table (8)	Comparison of subjects' comorbidities as regard AGEs among group 3	48
Table (9)	Correlation between AAD and AGEs among study groups	49
Table (10)	Correlation between ABI and AGEs among study groups	49

List of Figures

Fig. No.	*Subject*	*Page*
Fig. (1)	Alteration of different proteins via glycation (Persistently elevated glucose levels during long standing diabetes induce structural and functional changes in different protein in the body including albumin, globulins, fibrinogen and collagens.	١٠
Fig. (2)	The synthesis of advanced glycation endproducts (AGEs) is a non-enzymatic reaction where in its classical form the reactive carbonyl group of a sugar reacts with the nucleophilic amino group of an amino acid (e.g. arginine=Arg) or a protein ($R\text{-}NH_2$)	12
Fig. (3)	A typical Asteraceae flower head	32
Fig. (4)	Camellia japonica flower	33

ABSTRACT

BACKGROUND AND OBJECTIVES: In elderly diabetic patients, DM is associated with accelerated complications and exaggerated functional deterioration. It is known that AGEs are associated with predisposition to diabetic complications, however studying the effect of AGEs in elderly population with multiple comorbid diseases is little. The purpose of the study was to detect the relationship between advanced glycation end products and coronary risk factors, abdominal aortic diameter and peripheral arterial disease in elderly diabetics. SUBJECTS AND METHODS: case control study enrolled ninety elderly subjects who were divided into 3 groups thirty elderly diabetic subjects with comorbid diseases, thirty elderly diabetic subjects without comorbid diseases, and thirty healthy elderly subjects without diabetes as the control group. Each subject measured total AGEs level, abdominal aortic diameter at the level of iliac bifurcation, and ABI with hand held doppler. RESULTS : AGEs were higher in the control group than other groups, no significant correlation was found between AGEs and abdominal aortic diameter, and there was inverse correlation between AGEs and ABI among group with DM only. CONCLUSION: the use of plasma levels of AGEs as biomarkers for increased CVD risk in elderly may be limited and therefore alternative measurements of AGEs burden should be considered.

Keywords:

Advanced glycation end products, Elderly diabetics, oronary risks, abdominal aorta, peripheral arterial disease.

INTRODUCTION

Diabetes mellitus (DM) is a growing problem worldwide, because of long life expectancy and life style modifications ***(Chentli et al., 2015).***

Over the past 20 years, there has been an explosive increase in the number of cases of diabetes mellitus in both developed and developing countries ***(Khan et al., 2011).*** Moreover its prevalence and its co-morbidities and mortality are higher in elderly than in young people ***(Sloan et al., 2008).***

Diabetic complications appear to be multifactorial in origin, but in particular, the biochemical process of advanced glycation, which is accelerated in diabetes as a result of chronic hyperglycemia and increased oxidative stress, has been postulated to play a central role in these disorders ***(Goh and Cooper, 2008).***

Advanced glycation end products (AGEs) are produced through the non enzymatic glycation and oxidation of proteins, lipids and nucleic acids. Enhanced formation of AGEs occurs particularly in conditions associated with hyperglycaemia such as diabetes mellitus (DM) ***(Hegab et al., 2012).***

Elevated levels of circulating advanced glycation end products (AGEs) in the presence of hyperglycemia are believed to play a major role in the pathogenesis of macro-

vascular and micro-vascular diseases observed in diabetes mellitus ***(Ramasamy et al., 2012).***

Morbidity and mortality among people with diabetes mellitus are mostly triggered by premature cardiovascular disease (CVD) ***(Seshasai et al., 2011).*** AGEs are believed to have a key role in the development and progression of cardiovascular disease in patients with DM ***(Hegab et al., 2012)***.

Diabetes is a risk factor for peripheral arterial disease (PAD), and prevalence rates of 10–40% in the general population of patients with diabetes have been reported. Moreover, in comparison with subjects without diabetes, PAD is more likely to progress in patients with diabetes (***Hinchliffe et al., 2012).***

Patients with type 2 diabetes have a high risk for early and extensive development of peripheral arterial disease (PAD) and this excess risk is not explained by increased burden of traditional atherosclerotic risk factors ***(Malmstedt et al., 2015)***. Activation of the receptor for advanced glycation end products (RAGE) could be one additional mechanism for accelerated PAD and increased risk for amputation and death ***(Malmstedt et al., 2015).***

The risk of abdominal aortic aneurysms (AAAs) increases dramatically in the presence of the following factors: age older than 60 years, smoking, hypertension and Caucasian ethnicity ***(Aggarwal et al., 2011).***

The prevalence of diagnosed type 2 diabetes in men over 60 – the group most at risk of developing abdominal aortic aneurysms (AAAs) – is estimated between 10–15% ***(Wild et al., 2004).***

Receptor for advanced glycation end products (RAGE), can interact with a broad range of ligands. The binding of RAGE to its ligands induces cytokine production and inflammatory reactions, all of which are involved in the development and progression of AAAs ***(Fukami et al., 2014).***

On the other hand some epidemiologic evidences suggest that patients with diabetes may have a lower incidence of abdominal aortic aneurysm (AAA), but as diabetes is positively associated with most forms of vascular disease, the negative association with AAAs is seemingly paradoxical ***(Jamrozik et al., 2007).*** It is not known whether there is a negative relationship between diabetes and increasing aortic diameter below the aneurysmal range (<30 mm) or whether there is any association between aortic diameter and glycaemia ***(Jamrozik et al., 2007).***

Hence this research is aiming to detect the relationship between advanced glycation end products and coronary risk factors, abdominal aortic diameter and peripheral arterial disease in elderly diabetics.

AIM OF THE WORK

The aim of the study is to detect the relationship between advanced glycation end products and coronary risk factors, abdominal aortic diameter and peripheral arterial disease in elderly diabetics.

DEFINITION AND DESCRIPTION OF DIABETES MELLITUS

Diabetes is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. ***(American Diabetes Association, Diabetes Care 2010)***

Chronicity of hyperglycemia is associated with long-term damage and failure of various organ systems mainly affecting the eyes, nerves, kidneys, and the heart. ***(American Diabetes Association, Diabetes Care 2016)***

Type 2 DM which is more prevalent among elderly ***(Yakaryılmaz and Öztürk 2017***), is characterized by chronic inflammation and insulin resistance (IR), associated with chronically elevated oxidant stress (OS). ***(Vlassara and Uribarri, 2014)***

Epidemiology of DM:

Globally, an estimated 422 million adults are living with diabetes mellitus, according to the latest 2016 data from the World Health Organization (WHO**). *(WHO, 2016)***

The International Diabetes Federation (IDF) listed Egypt among the world top 10 countries in the number of patients with diabetes. In 2013, the IDF estimated that 7.5 million individuals have diabetes and around 2.2 million have prediabetes in Egypt. ***(Hegazi et al., 2015)***

Risk factors for type 2 diabetes include older age, obesity, family history of diabetes, impaired glucose tolerance and physical inactivity. ***(CDC, 2015)***

Diabetes mellitus among the Geriatrics population:

In old age (≥60 years old), DM is becoming an alarming public health problem, as for some authors one from two old persons are diabetic or pre-diabetic and for others 8 from 10 old persons have some dysglycemia ***(Chentli et al., 2015).***

In elderly patients, DM is associated with exaggerated functional deterioration that challenges the delivery of high-quality, individualized care. Most international clinical guidelines have ignored the often-unique issues of frailty, functional limitation, changes in mental health, and increasing dependency that characterize many aged patients with diabetes. ***(Dunning et al., 2012)***

While healthy older adults can use therapeutic approaches recommended for their younger counterparts, treatment plans for frail elderly patients need to be simplified and glycated hemoglobin and blood pressure goals need to be relaxed with the development of impairments in function, cognition, vision, and dexterity ***(Bansal et al., 2015).*** The goals of diabetes management in the elderly should be to maintain quality of life and minimize symptomatic hyperglycemia and drug side effects, including hypoglycemia. ***(Bansal et al., 2015)***