Study of Apolipoprotein E allele, Coronary Risk Factor and Cardiovascular Function in Asymptomatic Diabetic Elderly Patients

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Nesma Gamal Ahmed El Sayed El-Sheikh

Contents

List of Abbreviations

ABI	Ankle-brachial index
AD	Alzhiemer disease
APO E	Apolipoprotien E
AGEs	Advanced glycation end products
AMI	Acute myocardial infarction
APP-Aβ	Amyloid-β deposits
AT1	Angiotensin type 1 receptors
AT2	Angiotensin type 2 receptors
BMI	Body mass index
CAC	Coronary artery calcium
CAD	Coronary artery disease
CDC	Centers for Disease and Control Prevention
CRP	C-reactive protein
CVD	Cardiovascular diseases
DM	Diabetes mellitus
EASD	European Association for the Study of Diabetes
ECHO	Echocardiography
EF	Ejection fraction
FBS	Fasting blood sugar
G6PDH	Glucose-6-phosphate dehydrogenase
HDL	High density lipoprotein
HF	Heart failure
HTN	Hypertension

List of Abbreviations

IGF	Insulin-like growth factor
IL-6	Interleukin-6
IDF	International Diabetes Federation
IDL	Intermediate density lipids
LDL	Low density lipoprotein
LDLR	Low-density lipoprotein receptor
Lp-PLA2	Lipoprotein-associated phospholipase A2
LRP-1	Low density lipoprotein receptor-related protein-1
LVH	Left ventricular hypertrophy
PAFAH	Platelet-activating factor acetylhydrolase
PKC	Protein kinase C
PPBS	Postprandial blood sugar
TG	Triglycerides
VLDL	Very low density lipoprotein
PAI-1	Plasminogen activator inhibitor-1
PIP2	Phosphoinositol biphosphate
RAAS	Renin-angiotensin-aldosterone
RAGE	Receptor for advanced glycation end products
Synj1	Phosphoinositol phosphatase synaptjanin1
TNF-α	Tumor necrosis factor alpha
WHO	World Health Organization

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Abstract:

Aim: Study association between Apo E polymorphism and development of heart failure among diabetic patients.

Material and Methods: case control study conducted on 90 elderly participants and they were classified into three groups each had 30 participants first group diabetic with atherosclerotic complications, second was diabetics without any complications while third group was non diabetics as control all of them were subjected to assessment of blood sugar and lipid profile and Apo E allele detection as well as Echocardiography for assessment of heart failure.

Results: study showed that among diabetic patients with atherosclerotic complication there is increased incidence of heart failure more than diabetic without complications or non-diabetic patients and that incidence of heart failure is higher among those carrying Apo E4 allele.

Conclusion: the study concluded that Apo E4 allele is associated with increased risk of development of heart failure among diabetic patient mostly due to effect of Apo E4 on lipid metabolism and atherosclerotic process

Keywords: *Apolipoprotien E allele, heart failure, diabetes*

Introduction

Type 2 diabetes mellitus (T2DM) is one of the most common diseases with a high incidence and prevalence throughout the world. It affects nearly 4% of the world's population and this percentage will supposedly be increasing up to 5.4% by year 2025 ***(Chaudhary et al., 2012).***

Among diabetic patients a high prevalence of coronary heart disease is observed at a relatively young age. Thus, risk factors for atherosclerosis must be defined and avoided in patients with diabetes mellitus. Abnormality of lipids such as high triglyceride levels and low HDL cholesterol levels emerged as residual cardiovascular risks for diabetic patients ***(Ehara et al., 2012).***

Patients with type 2 diabetes mellitus have an increased incidence of atherosclerotic cardiovascular disease. This increase is attributable, in part, to associated risk factors, including hypertension and dyslipidemia. The latter is characterized by elevated plasma triglyceride levels, low levels of high-density lipoprotein (HDL) cholesterol, and small, dense low-density lipoprotein (LDL) particles ***(Ginsberg et al.,2010).***

Importance of searching for risk factors causing coronary heart disease (CHD) in diabetics arise from that macrovascular complications represent a major cause of mortality in type 2 diabetes, and MI and stroke accounting for about 80% of all deaths ***(Gudbjörnsdottir et al., 2011).***

T2DM is also known as a major independent risk factor for coronary artery disease (CAD) and is the major cause of morbidity and mortality affecting people with diabetes. To date, several mechanisms such as

dyslipoproteinemia, obesity, oxidative stress, smoking, exercise, alcohol intake, and genetic factors have been identified as risk factors of both T2DM and CAD. Lack of apolipoprotein E (apoE) gene has been clearly demonstrated as a leading cause of severe hyperlipidemia and spontaneous development of atherosclerosis in mammals ***(Chaudhary et al., 2012).***

Apolipoprotein E (apoE) is a multifunctional protein that plays a key role in the metabolism of cholesterol and triglycerides by binding to receptors on the liver to help mediate clearance of chylomicrons and very low-density lipoproteins from the bloodstream. Although individuals carrying the *ε4* allele have higher and those carrying the *ε2* allele have lower total cholesterol levels than people with the commonest *ε3/ε3* genotype, studies of lipid markers have typically involved too few participants to characterize relationships with different lipid subfractions across the 6 common genotypes. Different studies showed that compared with *ε3/ε3* individuals, *ε4* carriers have a much greater risk of coronary *disease* ***(Benet et al., 2007).***

Age and sex have been proposed as potential effect modifiers of the association between *APOE* and CHD risk because there is evidence that genotypic influence on mortality can vary by birth year and that estrogen and *APOE* may jointly affect lipid levels. Cigarette smoking, a well-established risk factor for CHD was also explored as an effect modifier between *APOE* genotype and CHD risk. It has been proposed that *apoe E4* carriers tend to produce a greater amount of LDLs, which makes them vulnerable to smoking-related increases in lipoprotein oxidation ***(Ward et al., 2009).***

Aim of the work:

To study the association between apolipoprotein E genetic polymorphism, coronary risk factors and cardiovascular function among asymptomatic diabetic elderly patient.

Chapter One

Apolipoprotein E (Apo E)

Introduction:

Human plasma has five different types of apolipoproteins (A, B, C, D, and E) and some of them are further categorized into subtypes ***(Eichner et al., 2002), (Anthopoulos et al., 2010).***

Apolipoprotein (Apo E) is a member of apolipoprotien gene family that was discovered in the 1970s and they are classified to three isoforms encoded by the E2, E3, E4 allele that were further subdivide into subforms giving six common isoforms of Apo E ***(Meigs et al., 2000), (Eichner et al., 2002), (Volcik et al., 2006)***, ***(Anoop et al., 2010).***

Apolipoprotein gene polymorphism has different effects on lipid metabolism and it is associated with certain lipid transport disorders, so it can play a role in different diseases that is why many researches were carried out aiming to understand their role in health and disease ***(Davignon et al., 1988), (Eichner et al., 2002), (Marrzoq et al., 2011).***

Shape and structure:

Plasma lipoproteins are spherical bodies composed of a nonpolar lipid core, primarily triglycerides and cholesteryl esters, with an external layer of phospholipids and apolipoproteins ***(Eichner et al., 2002) (Anthopoulos et al., 2010).***

Apolipoprotein is the only protein component that combine with free cholesterol, phospholipids, cholesterol esters, and some triacylglycerols to form lipoproteins ***(Eichner et al., 2002), (Anthopoulos et al., 2010).***

Apo E is a glycosylated protein it is associated with other plasma glycoproteins, such as high density lipoprotein (HDL), very low density lipoprotein (VLDL), and chylomicrons and it is also linked to the gene for low density lipoprotein (LDL) receptors ***(Anoop S et al., 2010), (Chaudhary et al., 2012)***, ***(Elmadbouh et al., 2013).***

The apolipoprotein gene is polymorphic resulting in 3 common alleles and 6 different genotypes which differ in amino acid sequence at positions 112 and 158, Apo E3 contains cysteine at 112 and arginine at 158 while Apo E2 has cysteine at both positions, and E4 has arginine at both sites ***(Volcik et al., 2006), (Chaudhary et al., 2012), (Ehara et al., 2012), (Elmadbouh et al., 2013).***

The amino terminal region of Apo E is responsible for its binding to the LDL receptor and the carboxy terminal mediates the binding of Apo E to surface lipoproteins which is influenced by specific amino acid differences ***(Anoop et al., 2010), (Marrzoq et al., 2011), (Elmadbouh et al., 2013).***

Apo E4 has one more positive charge while Apo E2 has one less, also Apo E2 and Apo E3 have reactive free sulfhydryl groups which can form disulfide bonds with other free sulfhydryl-containing proteins this may have important effects on the function of Apo E ***(Davignon et al., 1988).***