Study of APO E4, Coronary Risk Factors and Abdominal Aortic Diameter among Elderly Diabetic Patients

Thesis

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of M.D. degree in ***Geriatric and Gerontology***

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دراسة ال ApoE4 جين و مسببات تصلب الشرايين التاجية و قطر الشريان الاورطي البطني بين مرضى السكر من كبار السن

رسالة توطئة

للحصول على درجة الدكتوراه في طب المسنين وعلوم الاعمار

مقدمة من

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List of Abbreviations

2hPP	**:**	2 hour postprandial blood sugar.
AAA	**:**	Abdominal aortic aneurysm.
ACCF	**:**	American College of Cardiology Foundation.
ADL	**:**	Activities of daily living.
AHA	**:**	American Heart Association.
AIDS	**:**	Acquired Immunodeficiency Syndrome.
APAO	**:**	Antero-Posterior Abdominal Aorta Diameter.
APO E	**:**	Apolipoprotein E.
BMI	**:**	Body mass index.
BP	**:**	Blood Pressure.
CAD	**:**	Coronary artery disease.
CASS	**:**	Coronary Artery Surgery Study registry.
CCAIMT	**:**	Intima-media thickness of the common carotid artery.
CEP	**:**	Cholesterol Education Program.
CHD	**:**	Coronary heart disease.
CRP	**:**	C-reactive protein.
CV	**:**	Cardiovascular.
CVD	**:**	Cardiovascular disease.
DM	**:**	Diabetes mellitus.
ESRD	**:**	End-Stage Renal Disease.
FA	**:**	Fatty Acids.
FBG	**:**	Fasting Blood Glucose.
FBS	**:**	Fasting Blood Sugar.
FFA	**:**	Free fatty acid.
FMD	**:**	Brachial artery flow-mediated vasodilatation.
GDS	**:**	Geriatric Depression Scale.
GpIb	**:**	Glycoprotein Ib.
HAART	**:**	Highly active antiretroviral therapy.
HDL	**:**	High density lipoprotein.
HDL-C	**:**	High-density lipoprotein cholesterol.
HF	**:**	Heart failure.
HIV	**:**	Human immunodeficiency virus.
hs-CRP	**:**	High sensitivity C reactive protein.
HSPG	**:**	heparan sulphate proteoglycan.
HTN	**:**	Hypertension.
IADL	**:**	Instrumental activities of daily living.
IDL	**:**	Intermediate Density Lipoproteins.

IFG	**:**	Impaired Fasting Glucose.
IGT	**:**	Impaired Glucose Tolerance.
IL-1B	**:**	Interleukin-1B.
IL-6	**:**	Interleukin-6.
ISH	**:**	Isolated systolic hypertension.
ISHD	**:**	Ischemic heart disease.
LDL	**:**	Low density lipoprotein.
LDL-C	**:**	Low density lipoprotein cholesterol.
LDLR	**:**	LDL receptor.
LPL	**:**	Lipoprotein Lipase.
LVH	**:**	Left ventricular hypertrophy.
MI	**:**	Myocardial infarction.
MMSE	**:**	Mini-mental state examination.
NF-κB	**:**	Nuclear factor kappa-light-chain-enhancer of activated B cells.
NHLBI	**:**	National Heart, Lung, and Blood Institute.
NO	**:**	Nitric oxide.
OGTT	**:**	Oral Glucose Tolerance Test.
PAI-1	**:**	Plasminogen activator inhibitor-1.
PCR	**:**	Polymerase chain reaction.
PI-3	**:**	Phosphatidyl inositol.
PKC	**:**	Protein kinase C.
PPBS	**:**	Postprandial Blood Sugar.
PTH	**:**	Parathyroid Hormone.
RAGE	**:**	Receptors for advanced glycation end products.
REACH	**:**	Observational Reduction of Atherothrombosis for Continued Health registry.
RFLP	**:**	Restriction Fragment Length Polymorphism.
ROS	**:**	Reactive oxygen species.
T2DM	**:**	Type 2 diabetes mellitus.
TC	**:**	Total Cholesterol.
TG	**:**	Triglycerides.
TNF-a	**:**	Tumor necrosis factor-alpha.
VLDL	**:**	Very low density lipoprotein.
VLDL-C	**:**	Very low density lipoprotein cholesterol.
VSMC	**:**	Vascular smooth muscle cell.
WHO	**:**	World Health Organization.

Introduction

Diabetes mellitus is one of the most common diseases with a high incidence and prevalence throughout the world. World Health Organization (WHO) global prevalence of diabetes report estimated the prevalence of diabetes for all age-groups worldwide to be 2.8% in 2000 and 4.4% in 2030. The total number of people with diabetes is projected to rise from 171 million in 2000 to 366 million in 2030 ***(Wild et al., 2004)***.

Diabetes is common in the elderly population. More than 20% of adults aged 65 to 75 years and 40% of adults older than 80 years suffer from diabetes ***(Migdal et al., 2011)***.

Diabetes mellitus (DM) is an established risk factor for coronary heart disease; it confers a twofold increased risk for coronary heart disease, independent from other conventional risk factors ***(Sarwar et al., 2010).***

Genomics is revolutionizing biomedical research and providing great expectations with regard to disease prevention and treatment, several studies have identified genetic variants that predispose patients to common diseases ***(Guttmacher et al., 2007).***

APO E gene is one of the most studied genes which is responsible for stabilizing and solubilizing circulating lipoproteins in the body and also responsible for the development of Coronary artery disease (CAD) ***(Grundy, 2006).***

Previous studies have shown that APO E alleles have influence on the lipid clearance and metabolism in humans. APO E2 allele has been reported to be associated with higher plasma levels of APO E, decreased plasma levels of LDL cholesterol (LDL-C) and lower risk of CAD ***(Siest et al., 1995)*** while APO E4 is associated with lower plasma level of APO E, increased plasma levels of total cholesterol (TC), LDL-C, VLDL cholesterol (VLDL-C), and greater risk of CAD ***(Knouff et al., 1999).***

Results indicate that APO E4 allele has influence on lipid profile and is associated with the development of both T2DM with and without CAD ***(Chaudhary et al., 2012)***.

Atherosclerotic cardiovascular disease remains the major cause of morbidity and mortality in much of the world today ***(Mathers and Loncar, 2006).***

Presence and extent of calcified atherosclerosis in the abdominal aorta are significantly associated with increasing aortic diameter independent of the other cardiovascular risk factors ***(Allison et al., 2008)***.

The normal aortic diameter in adults usually ranges from 16 to 18 mm in women and 19 to 21 mm in men. Individuals with diameters outside this range seem to be at increased risk of other cardiovascular disease. There is a graded association between increasing aortic diameter and cardiovascular mortality ***(Norman et al., 2011).***

An Autopsy Study found that APO E polymorphism seems to be associated with atherosclerotic lesion area in both the coronary arteries and the aorta and demonstrated, at the vessel-wall level, that the APO E4 allele is a significant risk factor for Coronary heart disease ***(Ilveskoski et al., 1999).***

Information on the significance of APO E polymorphism in diabetic elderly subjects is limited and there are few studies of the effects of APO E on CVD in older diabetic people, and some studies revealed that in contrast to middle-aged subjects, the risk of cardiovascular disease in elderly subjects with APO E4 is not increased and others showed that the cardiovascular risk can be increased with APO E4 carriers.

Aim of the Work

- To determine the APO E gene polymorphism in diabetic elderly with and without cardiovascular complications compared to non diabetic elderly.
- To determine the association between APO E4 gene and coronary risk factors in diabetic elderly patients.
- To determine the association between APO E4 gene and abdominal aortic diameter in diabetic elderly patients.

Diabetes and Coronary Artery Disease in Elderly

Diabetes mellitus (DM) is a metabolic disorder with inappropriate hyperglycaemia either due to an absolute or relative deficiency of insulin secretion or reduction in the biologic effectiveness of insulin or both. It is also associated with disturbances concerned with protein, carbohydrate and lipid metabolism. The decreased uptake of glucose into muscle and adipose tissue leads to chronic extra cellular hyperglycaemia which results in tissue damage and chronic vascular complications in both types 1 and 2 DM ***(Amanullah et al., 2010)***.

In the Middle East and North Africa Region, 1 in 10 adults have diabetes. International Diabetes Federation estimates that there are 34.6 million people with diabetes in the Middle East and North Africa, a number that will almost double to 67.9million by 2035 if concerted action is not taken to tackle the risk factors fuelling the epidemic of diabetes throughout the Region ***(International Diabetes Federation, 2013).***

Diabetes prevalence was found to be 20.0% in urban Egypt. Diabetes prevalence was significantly higher in urban areas than in rural areas. Undiagnosed diabetes is common in Northern Africa with a prevalence ranging from 18% to 75%. The prevalence of chronic diabetes

complications ranged from 8.1% to 41.5% for retinopathy, 21% to 22% for albuminuria, 6.7% to 46.3% for nephropathy and 21.9% to 60% for neuropathy ***(Manouk and Charles, 2013).***

In a study done in Egypt, the crude prevalence rate of known diabetes was 4.07% it increased with age to reach 19.8% among females aged 50-59. 13.3% of males had a history of myocardial infarction or stroke. ***(Arafa and Amin, 2010).***

Diabetes is common in the elderly population. More than 20% of adults aged 65 to 75 years and 40% of adults older than 80 years suffer from diabetes ***(Migdal et al., 2011).***

Diabetes mellitus is the fourth leading cause of death by disease globally and is the leading cause of blindness and visual impairment in adults in developed countries ***(Brussels, 2003)***.

85 to 90% of total diabetic population has type 2 diabetes whereas 10% to 15% have type 1 diabetes ***(Sherwin, 2000).***

Hyperglycemia that is not sufficient to meet the diagnostic criteria for diabetes mellitus, is categorized as either Impaired Fasting Glucose (IFG) with Fasting Blood Glucose (FPG) ranges 100-125 mg/dL or IGT (impaired

glucose tolerance) with 2 hours plasma glucose ranges 140-199 mg/dl ***(American Diabetic Association, 2015)***.

Recently, IFG and IGT have been officially termed prediabetes and both are considered as risk factors for future diabetes and cardiovascular disease ***(American Diabetic Association, 2015)***.

Criteria for the Diagnosis of Diabetes Mellitus:

(1) Hemoglobin A1C ≥6.5%.
Or

(2) FPG ≥126 mg/dl (7.0 mmol/l). Fasting is defined as no caloric intake for at least 8 h.
Or

(3) 2-hr plasma glucose ≥200 mg/dl (11.1 mmol/l) during an OGTT. The test should be performed as described by the World Health Organization, using a glucose load containing the equivalent of 75g anhydrous glucose dissolved in water.
Or

(4) In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥200 mg/dl (11.1 mmol/l).

In the presence of equivocal hyperglycemia, criteria 1–3 should be confirmed by repeat testing ***(American Diabetic Association, 2015)***.

Diabetes mellitus (DM) is an established risk factor for coronary heart disease; it confers a twofold increased risk for coronary artery disease, independent from other conventional risk factors ***(Sarwar et al., 2010).***