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ASSOCIATION BETWEEN APOLIPOPROTEIN E GENE POLYMORPHISM AND HEART FAILURE AMONG DIABETIC ELDERLY PATIENTS

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Apolipoprotien E allele, heart failure, diabetes.

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

Introduction

Diabetes mellitus is one of the most common diseases with a high incidence and prevalence throughout the world and its prevalence increases every year so it will reach 5.4% by year 2025 and this will be associated with increase diabetic complications as cardiovascular diseases and so increase mortality **(1) (2) (3).**

Recently cardiovascular diseases among diabetics has increased dramatically in both developed and developing countries due to change in life style and dietary habits **(4) (5)**

The Middle East and North Africa Region is considered one of the areas with highest prevalence of diabetes as it represented 10.9% at year 2012, and it is expected to be reach 59.9 million by year 2030 (**5)**

Egypt will I have at least 8.6 million adults with diabetes by year 2030 as diabetes will become the eleventh most important cause of premature mortality and the sixth most important cause of disability burden **(4).**

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Elderly population have high prevalence of diabetes as it estimated that 20% of those that are 75 years or older will have diabetes and this will increase incidence of diabetic complication and mortality and morbidity **(6).**

Diabetes mellitus it is responsible for the occurrence of cardiovascular diseases as coronary artery disease (CAD) and cardiac heart failure (CHF) both systolic and diastolic types that will affect quality of life and increase mortality and morbidity **(7).**

Diabetes mellitus increase risk cardiovascular complications through several mechanisms the most important is atherosclerotic process so that explains why Patients with known atherosclerotic disease (coronary, cerebral, or peripheral blood vessels) are likely to develop HF **(2) (8) (9) (10) (11) (12).**

Other mechanisms that explains the occurrence of Heart failure among diabetic patient are stiffening of the myocardium due to cross-linking and extracellular matrix deposition, hypertrophy, and neuronal abnormalities **(7)**.

Diabetes mellitus is usually associated with other comorbidities such as abdominal obesity, hypertension, dyslipidemia, age, sex, positive family history, and smoking that when they coexist they increase the risk of diabetic macrovascular complications and increase mortality so aggressive treatment of diabetes and associated coronary risk factors is recommended **(13) (14) (15) (16).**

American Diabetic Association 2013 recommended that cardiovascular risk factors among diabetics should be assessed at least annually and if detected should be treated and that older adult that are functional, cognitively intact, and have significant life expectancy should be screened as young adults and receive the same diabetes care with similar goals **(7) (8).**

Heart failure is still considered one of the diseases with high mortality worldwide although the management of heart failure has improved dramatically, so many studies searched for associated risk factors such as hypertension, lipid disorders, obesity, diabetes mellitus, and smoking and once detected will be treated and so decrease mortality **(8) (17)**.

One of the factors that was thought it could play a role in risk of atherosclerotic disease and heart failure is the genetic factors and one of these genetic factors is Apo E gene as studies showed that Lack of apolipoprotein E (apo E) gene causes severe hyperlipidemia and spontaneous development of atherosclerosis **(1).**

Apolipoprotein (APO) E a member of apolipoprotein gene family and there is three isoforms encoded by the ε2, ε3, and ε4 which are further subdivided to six subforms **(18) (19) (20).**

Apolipoprotein E plays a role in lipid metabolism by acting on different receptors and maintain integrity of lipid particles, act as cofactor in some enzymatic reactions, act on hepatic binding, uptake, and catabolism of lipid particles also act on absorption of dietary fat and cholesterol level uptake of postprandial lipoprotein particles results in differences in regulating hepatic low density lipoprotein (LDL) receptors among different alleles , which in turn contributes to genotypic differences in total and LDL cholesterol levels **(1)(19) (20) (21) (22)**

Different Apo E polymorphism have different effect on LDL and cholesterol level as Apo e4 allele increases LDL cholesterol and e2 allele decreases LDL cholesterol levels so this allelic variation plays role in development of atherosclerotic diseases as coronary artery disease and heart failure **(20) (23) (24)**

Studies carried on Apo E gene polymorphism show that it also can increase oxidative stress in hyperglycemia and reduced lipid clearance so develops insulin resistance and DM and also cause vascular inflammation leading to atherosclerosis through release of several cytokines causing higher risk of developing CAD and heart failure **(1) (21).**

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Studies linked Apo E4 allele with development of heart failure as it is associated with higher plasma cholesterol levels and risk of coronary artery disease, and also decreased antioxidant activity of the Apo E4 allele may represent a genetic risk factor for the development of myocardial dysfunction and heart failure **(**9**) (17)**.

Aim

The study was conducted to investigate association between apolipoprotein E genetic polymorphism and risk of heart failure among diabetic elderly patient

Materials and methods

Study design*:*

A Case control study conducted on 90 elderly patients aging 60 years old or more and was classified to three groups

- Group A: 30 diabetic patients with atherosclerotic complications (mainly coronary artery disease)
- Group B: 30 diabetic patients with no atherosclerotic complications
- Group C: 30 non diabetic patients

Methodology

All patients will be subjected to

1. ***History taken and examination***
2. ***Comprehensive geriatric assessment***
3. ***Investigations:***
   a) *Laboratory*
      - Fasting and 2hr post prandial blood glucose level
      - Lipid profile (TG, Total cholesterol, HDL, LDL).
      - Apolipoprotein E gene polymorphism
   b) *Cardiovascular function:*
      - Echocardiography

Results

The study is conducted on 90 elderly patient classified into three groups the participant ranged from 60 to 86yrs old and the three groups were matched as regard age and gender, as regard Smoking history they were classified to current smoker, exsmoker and nonsmokers and there was no statistical difference between the three groups as smoking **(Table 1)**

Echocardiography was done to all patient and the EF was assessed and the results was compared between the three groups showing that mean **EF%** was significantly lowest in group-**A (45.6%),** followed by group-B **(60.1%)** and highest in control group **(65%) (Table 1)**.

Assessment of Apo E polymorphism among the study showed that among group A [18 participant carried (Apo E3) and 12 participants carried (Apo E4)], while group B had [16 participants carrying (Apo E2), 3 participants carried (Apo E3) and 11 participants carried (Apo E4)] while Control had [14 participants carried (Apo E2),7 participants carried (Apo E3) and 9 participants carried (Apo E4) and by comparing the three groups together as regard APO E polymorphism show that: Group-A had highest frequencies of E3 and E4 than group B and C, with no significant difference between group-B and control group. **Table (1).**

As regard lipid profile between the different groups there was higher level of cholesterol and LDL among group B and A compared to control group while comparing the two diabetic groups their level is higher among group B **Table (1).**

Ejection fraction was measured to detect systolic heart failure and was compared among the three groups showing that systolic heart failure is significantly higher among group A followed by group B **(Table 2)**

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ECHO also was used to detect diastolic function showing that diastolic heart failure is significantly higher among group A (**Table 2)**

Among the current study assessing the association between heart failure and Apo e polymorphism among group A showed that Higher percentage of APO E4 was among cases with heart failure, followed by APO E3 and the difference is significant statistically while no significant difference between group-B and group C as regard association between Apo E alleles and echocardiography findings (EF and diastolic dysfunction) **(Table 3)**

Table (1): Demographic characteristic, lipid profile, Echocardiographic finding and Apo E distribution among the study population:

Variable		Group A (N=30)	Group B (N=30)	Control (N=30)	$P_{A/B}$	$P_{A/C}$	$P_{B/C}$
Age	Mean±SD	65.4±6.6	65.3±6.6	67.2±6.4	0.969	0.285	0.268
	Range	60.0-85.0	60.0-86.0	60.0-82.0			
Sex (N, %)	Female	21 (70.0%)	21 (70.0%)	17 (56.7%)	1.000	0.284	0.284
	Male	9 (30.0%)	9 (30.0%)	13 (43.3%)			
Smoking	Current	5 (16.7%)	8 (26.7%)	6 (20.0%)	0.860	1.000	0.552
	Ex	5 (16.7%)	3 (10.0%)	4 (13.3%)			
	Never	20 (66.7%)	19 (63.3%)	20 (66.7%)			
ECHO (EF %)	Mean±SD	45.6±15.4	60.1±7.2	65.0±5.3	0.001*	0.001*	0.004*
	Range	20.0-74.0	30.0-70.0	59.0-84.0			
e22, e23	N (%)	0 (0%)	16 (53.3%)	14 (46.7%)	0.001*	0.001*	0.380
e33	N (%)	18 (60%)	3 (10%)	7 (23.3%)			
e34, e44	N (%)	12 (40%)	11 (36.7%)	9 (30%)			
Cholesterol(mg/dl)	Mean±SD	161.7±56.9	191.0±62.3	190.9±55.1	0.062	0.048*	0.991
	Range	62.0-300	93.0-350	95.0-299			
TG (mg/dl)	Mean±SD	135.8±70.8	151.6±76.6	146.4±76.2	0.411	0.580	0.793
	Range	35.0-335	68.0-400	38.0-391			
LDL (mg/dL)	Mean±SD	92.0±36.6	112.0±47.8	108.2±43.9	0.075	0.128	0.750
	Range	21.0-196	35.0-219	47.0-230			
HDL (mg/dL)	Mean±SD	33.6±13.1	38.0±11.1	46.8±14.3	0.165	0.001*	0.009*
	Range	8.0-71.0	11.0-65.0	16.0-73.0			

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(*)Indicates that p value is statistically significant

Table (2): Heart failure among study groups:

HEART FAILURE		GROUP						Chi-Square	
		Group A		Group B		Control			
		N	%	N	%	N	%	X^2	P
SYSTOLIC HF	YES	13	43.33	1	3.33	0	0.00	26.560	0.001*
	NO	17	56.67	29	96.67	30	100		
DIASTOLIC HF	NO	24	80.00	30	100	30	100	12.857	0.002*
	YES	6	20.00	0	0.00	0	0.00		

(*)Indicates that p value is statistically significant

Table (3): APO E alleles in each group and echocardiography findings:

	Variable	APO E			P
		E2	E3	E4	
Group A	Mean EF%	---	46.8±16.5	43.8±14.2	0.600
	HF(systolic & diastolic)	---	8 (44.4%)	10 (83.3%)	0.058*
Group B	Mean EF%	58.1±8.9	61.3±1.1	62.5±3.8	0.294
	HF(systolic & diastolic)	1 (6.2%)	0(0%)	0(0%)	0.636
Group C	EF%	65.4±5.9	63.3±4.4	65.8±5.1	0.322

(*)Indicates that p value is statistically significant

Discussion

The current study aimed to assess the relation between APO E polymorphism, and cardiovascular function in elderly diabetics. Ninety participants were involved in the study and were subdivided into three groups and they were matched as regard age, gender.

Regarding ECHO finding the current study showed that diabetic participants had lower ejection fraction compared to control group, and group A had lower ejection fraction than group B this reflect the poor cardiac function among the diabetic population and it is worst among those with atherosclerotic diseases (as coronary artery disease).

Among the current study Echocardiography results showed that higher rates of both diastolic and systolic heart failure was among group A, followed by group B, since Diabetes is associated with increased risk of cardiovascular disease as (coronary artery disease and impaired cardiac function, predominantly diastolic dysfunction)

As regard lipid profile between the different groups showed that higher level of cholesterol and LDL is among group B and A compared to control group while comparing the two diabetic groups their level is higher among group B probably because group A has experienced diabetic atherosclerotic complication so they are receiving lipid lowering drugs

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By studying the distribution of Apo E allele among each group showed that group A had highest frequency of Apo E4 and none of the participants has Apo E2 however group B and group C had frequencies of Apo E2 53%, 46% respectively

The current study showed significant association between Apo E polymorphism and ejection fraction as results showed that lower ejection fraction is among carriers of Apo E4, and that carriers of Apo E4 allele have more risk of development of heart failure (both systolic and diastolic heart failure) this is usually occurs due to function of Apo E4 and its effect on lipid metabolism in the body resulting in increases level of LDL and total cholesterol and so increase risk of atherosclerotic complications among diabetics

Due to effect of Apo E allele on development cardiovascular diseases among diabetics so early screening of these patients for Apo E allele and other cardiovascular risk factors and control them early so we can decrease the incidence of diabetic complications so decrease mortality and morbidity and so improve quality of life.

Conclusion

Many coronary risk factors participate in development of cardiovascular disease among diabetic patients one of these risk factors is Apolipoprotein E allele as the current study linked association between development of heart failure and Apo E4 allele and this is thought to be explained by several mechanisms one of it is the effect of APO E4 on lipid metabolism in body as it increases level of LDL and total cholesterol and stimulate the atherosclerotic process.

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