

REVIEW ARTICLE

Apolipoprotein E: A Possible Predictor Risk Factor For Cardiovascular Disease

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ABSTRACT

Apolipoprotein E (apoE) polymorphism is a human genetic risk factor and has been well-established to be associated with Alzheimer's disease, lipid abnormalities, and cardiovascular disease (CVD). ApoE gene polymorphism is reported to correlate with lipid metabolism disturbances and coronary artery stenosis. Furthermore, $\epsilon 4$ allele carriers were found to have poor prognosis in survival rates of post-myocardial infarction. The purpose of the review is to distinguish the possible of apoE gene polymorphism as a determinant for CVD and its association. Preliminary data suggest $\epsilon 4$ allele carrier identification could be beneficial for risk stratification of CVD and initiation of statin therapy as primary intervention. Numerous studies have been done, however, results varied between studies as well as in different population. The evidence presented herein can help describe the risk prediction based on apoE gene polymorphism.

Keywords: Apolipoprotein E, Cardiovascular disease, LDL

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INTRODUCTION

According to World Health Organization (WHO), cardiovascular diseases are major health problems globally with approximately 17.9 million deaths each year, by which more than 80% of deaths are related to cardiovascular diseases (e.g. heart attacks and strokes). Cardiovascular diseases (CVD) are caused by various factors such as unhealthy lifestyle and diet, as well as inadequate physical activity (1). CVD is also known to be a complex genetic trait that involves multiple genetic and environmental components (2), hence, other than poor diet intake or lack of exercise, genetic variants can also predispose to CVD. Therefore, many studies were done to assess the genetics of CVD, and this includes apolipoprotein E gene polymorphism.

APOE AND LOW-DENSITY LIPOPROTEIN (LDL)

Apolipoprotein E is a combination of protein and lipids to form lipoproteins that carry cholesterol and fats through the bloodstream (3). The gene, which is located on chromosome 19, is responsible to encode the protein, known as apoE gene. It describes three alleles of $\epsilon 2$, $\epsilon 3$, and $\epsilon 4$ (4). These alleles will further establish by the six

genotypes; $\epsilon 2/\epsilon 2$, $\epsilon 4/\epsilon 2$, $\epsilon 3/\epsilon 2$, $\epsilon 3/\epsilon 3$, $\epsilon 4/\epsilon 3$, and $\epsilon 4/\epsilon 4$ (5). This genetic variation can influence plasma lipid levels and such polymorphisms contribute to the pathogenesis of atherosclerosis that leads to developing of coronary heart disease (6). Some studies showed, $\epsilon 4$ is linked to the increased level of low-density lipoprotein (LDL) cholesterol and the risk of CVD, while $\epsilon 2$ is associated with the decrease in LDL cholesterol level (7).

Since apoE gene is closely linked to the lipid levels in the body, it is very essential to know how lipid levels can contribute to the increased risk of developing CVD. A retrospective study by Marzooq et al. (8) on randomly selected 137 subjects – 69 having coronary heart disease (CHD) and 68 healthy subjects – whereby their blood samples were analysed for lipid profiling and apoE genotyping. The results revealed a significantly increased LDL level in the case group and no significant difference in the total cholesterol. Therefore, this likely describe that LDL cholesterol is associated with the risk of CVD. On a side note, the mean cholesterol level observed was higher in $\epsilon 4$ genotype followed by $\epsilon 2$ and $\epsilon 3$, thus reaffirming that apoE gene polymorphism does affect the lipoprotein levels in the body. It is also observed that $\epsilon 4$ allele had influence on LDL synthesis in the liver, hence, having relationship to the higher level of total cholesterol (TC) and LDL that leads to the prevalence of atherosclerosis which was comparable to the results by Marzooq et al. (8). Thus, this may explain why high level of LDL is the primary cause towards developing

of coronary heart disease irrespective other risk factors.

APOE AND DIABETES MELLITUS

On the other hand, Massimo et al. (9) accomplished a study among diabetic patients to determine apoE polymorphism as a risk factor. The study involved random 517 Italian diabetic patients whereby 81 of them had type 1 diabetes mellitus (T1DM) and 436 had type 2 diabetes mellitus (T2DM). The study determined vascular disease were at the time of recruitment and four years interval. From their observation, there was no significant difference of incidence between diabetic patients in all apoE phenotypes. It was found that $\epsilon 4$ did not significantly characterized the factor for vascular disease in Italian diabetic patients and cannot be universally considered to contribute to the disease. Therefore, they suggested that an additional study to be carried out with different populations to further clarify the finding (9).

Regarding the apoE $\epsilon 4$, another study was done to determine if $\epsilon 4$ allele is a risk predictor for coronary heart disease death among T2DM patients. Xiang et al. (5) recruited 36 T2DM with $\epsilon 4/\epsilon 4$ or $\epsilon 4/\epsilon 3$ from January 1993 to December 1999, whereas 62 patients were recruited with $\epsilon 3/\epsilon 3$, and 33 with $\epsilon 2/\epsilon 2$ or $\epsilon 3/\epsilon 2$ genotypes. A follow-up study was carried out in 3 to 10 years with the results showing serum TC and LDL level were observed to be higher in subjects with $\epsilon 4/\epsilon 3$ or $\epsilon 4/\epsilon 4$ compared to subjects with $\epsilon 2/\epsilon 2$ or $\epsilon 3/\epsilon 2$. During the follow-up period, few patients who died from CHD was recorded to make comparison. It was observed that the mortality rate was higher among patients with $\epsilon 4/\epsilon 3$ or $\epsilon 4/\epsilon 4$ genotypes. Logistic analysis was carried out for the whole population that revealed $\epsilon 4$ allele and $\epsilon 2$ allele were independently and significantly related to deaths from CHD. However, the underlying justification behind the apoE association and the increased risk of CVD death among T2DM patients was still uncertain (5). This may explain the association between the apoE $\epsilon 4$ allele with the increasing risk of CVD death especially in elderly patients with T2DM. A follow-up study to confirm apoE $\epsilon 4$ allele as a risk predictor of CHD deaths in T2DM patients was recommended (5).

Another study by El-Lebedy, Raslan and Mohammed (10) was carried out to investigate the correlation between apoE gene polymorphism with lipid profile and CVD among diabetic patients. A total 284 subjects were recruited in the study which was further categorized into three groups. The control group were subjects with no T2DM. The next group included T2DM patients without history or signs of CVD. Another group of patients recruited were 100 T2DM subjects with CVD or any of vascular diseases.

From the result, it is clear that apoE $\epsilon 3/\epsilon 3$ genotype was prevalent. But $\epsilon 3/\epsilon 4$ genotype $\epsilon 4$ allele was found

to be high in patients with CVD. It is also observed that there was a relationship between $\epsilon 3/\epsilon 4$ with CVD development among diabetic patients. This possibly due to lipid metabolism which may be involved in atherogenesis (10). Another study by Rajesh et al. (11) also demonstrated that apoE $\epsilon 4$ allele was strongly related to lipid profile among T2DM and CVD patients. This finding was also supported by previous study that revealed apoE is another probable cofactor and lipid profile is a predictive value for CVD (9,12).

Hence, the outcomes of this study disclose that apoE gene polymorphisms do have association with CVD, and apoE $\epsilon 4$ allele was identified as a non-dependent risk factor for both T2DM and CVD patients (10).

APOE AND CARDIOVASCULAR DISEASE

Zülküf et al. (13) did a study that specifically assessed the relationship between apoE gene polymorphism with the severity of coronary artery disease. The study selected 138 patients with acute myocardial infarction and blood samples were analysed for genotyping and fasting lipid profile which included total cholesterol, HDL cholesterol, and triglyceride levels. The assessment for severity of coronary atherosclerosis was based on Gensini score. The results reported patients with acute myocardial infarction showed no statistical difference between the severity of coronary artery disease and apoE gene polymorphism. However, they found that the lipid profile was indicated to be high in the patients that carried apoE 3/4 genotype and apoE4 allele. Hence, this provides another evidence that $\epsilon 4$ allele indeed closely related to the risk of developing CVD.

The incidence of the $\epsilon 4$ allele is doubly high among patients who succumb to coronary heart disease (14). In contrast, a study conducted by Kuusisto et al. showed that allele $\epsilon 4$ reduced the risk of developing cardiovascular disease in the elderly (15). Consequently, the allele $\epsilon 4$ cannot be justified as a significant risk factor for cardiovascular disease especially in the elderly. However, Bishwa et al. suggested a satisfactory impact of apoE genetic divergence susceptibility to cardiovascular disease (16).

CONCLUSION

ApoE gene polymorphism does have an association with the risk of developing CVD. Among the three alleles, $\epsilon 4$ carries is closely related to altered lipid metabolism in the body, thus having the greater the risk of having CVD compared to $\epsilon 2$ and $\epsilon 3$ allele. Even so, $\epsilon 4$ allele cannot be solely considered to predispose to CVD as there are many other risk factors that should be taken into accounts. Despite numerous studies, it is still complicated to find the correlation between apoE4 and coronary heart disease. In fact, the difference in human population may also influence in determining of apoE

gene polymorphism as an associated factor for CVD, therefore, it is essential to carry out an extensive study to provide a solid explanation on the genetic variation and its impact on the disease occurrence.

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