REVIEW ARTICLE

# Apolipoprotein E Gene, Type 2 Diabetes Mellitus and Cardiovascular Disease: A Review of the Literature

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## ABSTRACT

The incidence of diabetes in Malaysia rose dramatically year by year. Diabetes mellitus (DM) is a significant general health issue and the disease contains a higher possibility to steer into a cardiovascular complication. Besides, a poor management of DM can contribute to lipoprotein metabolism modifications. The Apolipoprotein E (APOE) gene is widely acknowledged for its crucial function in the process of lipid metabolism and the potential risk of cardiovascular diseases (CVD). The role of APOE in lipid metabolism has been thoroughly recognized. In this review, information from different studies on APOE gene polymorphism, T2DM and CVD are summarized and discussed. Various studies on APOE gene polymorphisms have been published. However, the studies are still minimal and remain unclear. Therefore a better understanding of the remarkable APOE polymorphism and trends might help to identify the association and provide strong clarification on CVD and T2DM.

**Keywords:** Apolipoprotein E, Polymorphism, Type 2 Diabetes Mellitus, Cardiovascular Disease

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## INTRODUCTION

The populace's development in the ongoing years has led to a chronic disease situation due to the development flow. The most-risky issue we are confronting today is DM in most countries worldwide. From previous studies, the definitions of DM have been developed. Most international expert groups stated that DM is a widespread metabolic abnormality and is characterized by hyperglycaemia, which is caused by insulin resistance or the pancreas's failure to produce adequate amounts of the hormone insulin and thus causing an increase in glucose levels in blood (1). There was an estimated over million adult individuals with undiagnosed diabetes in Malaysia. The National Health and Morbidity Survey (NHMS) 2019 reported that prevalence of T2DM is increased 1.1% with almost 2 million adult individuals with known diabetes in Malaysia (2). The International Diabetic Foundation (IDF) predicts Malaysia will be listed top ten states with the most elevated pervasiveness of diabetes among people aged 20 until 79 years old by 2030 (3). While World Health Organization (WHO), in the 'Global Status Report on Noncommunicable Diseases 2014', reported that the prevalence of diabetes among Malaysian adults is 11.1%, which is 1.2 times higher than the global prevalence (4). World Health Organization (WHO) assessed that Malaysia consists of 2.48 million diabetics by 2030 (5). Factors such as family history, age, lack of physical activities, obesity and other diseases may increase DM's chances (6). Long-term DM and poor management can lead to a specific form of alteration in lipoprotein metabolism that are responsible for atherosclerosis (7). Plasma lipid alterations in patients with T2DM were related to coronary artery disease (CAD), cerebrovascular disease and nephropathy (8). Because of its well-established ties to Alzheimer's dementia, dyslipidemia and CAD, the APOE polymorphism has been thoroughly studied as a genetic risk factor in humans (9,10). APOE polymorphism has been disclosed to associate lipid metabolism disturbances and with coronary artery stenosis. Several studies have been carried out to determine the CVD risk prediction development based on APOE gene polymorphisms in diabetic patients. This review aimed to discuss the association within APOE polymorphisms and T2DM and CVD.

## APOE AND DIABETES MELLITUS (DM)

Apolipoprotein E (APOE) is a glycoprotein presence in very-low-density lipoprotein (VLDL), intermediate-density lipoprotein (IDL), high-density lipoprotein (HDL), chylomicron and chylomicron remnants, located on chromosome 19. APOE is part of the Apolipoprotein gene family, which included APO (A-I), APO (A-II), APO (A-IV), APO (C-1), APO (C-II) and APO (C-III) (11). There are four exons and three introns in the APOE gene,

totalling 3597 nucleotides that encode 299 amino acid polypeptides (12). The most frequent alleles were ε2, ε3 and ε4 alleles. APOE ε3 consists of cysteine at 112 and arginine at 158. APOE ε2 encloses cysteine at position 112 and 158, and ε4 has arginine at 112 and 158 (13). Based on the alleles mentioned, the ε3 allele is the top widely recognized and can be noticed over 80% of the public population, followed by ε4 and ε2 (14). These alleles code for three isoforms, and genotypes ε2/ε2, ε4/ε2, ε3/ε2, ε3/ε3, ε4/ε3, and ε4/ε4, respectively were determined by Luo et al. (15).

Type 2 Diabetes Mellitus (T2DM) is an ordinary chronic metabolic disorder inclining to cardiovascular disease (CVD), which could prompt heart failure through an assortment of causes, including myocardial infarction and chronic pressure overload (16). The cause of DM is multifactorial. Since the APOE gene is firmly related to DM, it is very important to understand the risk factors for CVD. Martín-Tímon et al. (17) split the risk factors in DM into two categories, traditional and non-traditional risk factors in Table I.

In Saudi Arabia, 898 genetically unrelated Saudi individuals were chosen for a case-control study, including 438 T2DM patients and 460 healthy patients (18). The case and control groups' genotype and allele frequency distributions were assessed using the direct counting method. The APOE ε2 allele is linked to both lipid profile and T2DM, according to their findings. The ε4 allele was also detected to be a reliable predictor of lipid status, and they appear to be a correlation within ε4 and T2DM, along with obesity. As a result, APOE polymorphism plays a significant role in the risk of T2DM patients. Overall, the study exhibited that APOE polymorphisms are linked to a higher risk of T2DM in Saudi (18).

A total of 102 participants were enrolled in an analytic analysis by Rahman et al. (19), 51 in the diabetes group and 51 in the non-diabetes group. Enlistment was restricted to Malaysians aged 40 and up. The objective was to discover whether there was a relationship between the frequency of the APOE allele and fasting glycemic status in T2DM patients. The findings revealed e2 and e4 alleles were slightly higher among the subjects with T2DM. But, there was no significant association between APOE alleles and T2DM. This probably due to scarcity sample size.

Previous study by Luo et al. (15) discovered the relationship between APOE gene (ε2/ε3/ε4) polymorphisms and CVD vulnerability in individuals with T2DM. According to the findings, the APOE gene is closely linked to individuals who have diabetes instead of healthy individuals. Moreover, in patients with T2DM, the APOE gene ε4 mutation is linked to an elevated risk of CAD, while the ε2 variation does not correlate with the disease. Further investigations with greater sample size and incorporated with the gene-environment association is required to definitively relationship between the APOE gene ε2/ε3/ε4 polymorphisms and CAD risk development in patients with T2DM. On the other hand, another study by Irie et al. (20) have also affirmed Luo's discoveries.

In addition, Peila et al. (21) conducted a study in which 2574 participants participated, 70% of whom were considered non-diabetic and the rest were determined to have diabetes. The inquiries are focused on a wide number of members and have been populace-based. The blood sample was analysed for genotyping by PCR and fasting lipid profile by FBG test, including total cholesterol (TC), triglycerides (TG), high-density level (HDL) and low-density level (LDL). The outcomes were summed up that those with diabetes have a slightly greater chance of CVD. The association between diabetes and APOE polymorphism is particularly clear between carriers of the APOE ε2 allele.

Almost all studies were conducted to prove a causal relationship between APOE gene polymorphism and the risk of T2DM were found relatively significant

## APOE AND CARDIOVASCULAR DISEASE (CVD)

CVD is the outstanding cause of death globally, computing for over 80% of all deaths each year. These situations are expected to rise in the coming years. The APOE ε2 and APOE ε3 alleles increased slightly the heart disease risk (22).

Mooijaart et al. (23) led a study into the relation between APOE genotype and CVD risk in old age. This way, 546 of the total subjects were selected randomly. Regardless

**Table 1: Types of risk factors in DM**

| Traditional Risk Factors | Non-Traditional Risk Factors |
|---|---|
| Dyslipidaemia | Insulin resistance and hyperinsulinemia |
| Blood pressure | Postprandial hyperglycaemia and glucose variability |
| Obesity and abdominal obesity | Microalbuminuria |
| Physical exercise | Haematological and thrombogenic factors |
| Smoking | Inflammation |
| | Homocysteine and vitamins |
| | Erectile dysfunction |
| | Genetics and epigenetics |

of APOE genotype or plasma lipids, high plasma APOE levels precede an increase in circulating C-reactive protein (CRP) and strongly correlate with CVD mortality in the elderly. Carriers of the ε2 or ε4 alleles were found to have similar mortality risks. Because of lifestyle changes, selective survival, or age-related physiologic changes, CVD risk factors tend to change with age changes (24). Different roles for the APOE alleles in survival by gender in old age are needed in future studies, according to Rosvall et al. (25).

Having said that, Marrzoq et al. (26) conducted a study among 137 subjects chosen at random, including 69 Coronary Heart Disease (CHD) patients. They found that APOE ε3/ε3 genotype was found to be the greatest widespread in both the control and CHD categories. APOE ε2/ε3 and APOE ε4/ε3 are among the most common genotypes. There were no significant differences in APOE genotypes between both groups.

## APOE IN CARDIOVASCULAR DISEASE (CVD) AND DIABETES MELLITUS (DM)

The previous study by Sudong Liu, Jing Liu and the other three researchers (27) explored the development of APOE gene polymorphism and CVD risk among subjects with T2DM. An aggregate of 924 subjects has participated in this cross-sectional analysis. Statistical analysis was evaluated by univariate and multivariate logistic analysis to interpret the correlation of disease and risk factors. The results showed ε3/ε4 was increased among subjects with T2DM and CVD. The subjects with CVD had a higher amount of ε4 allele than the controls. In Malaysia, Ashari et al. (28) explored the link between APOE gene polymorphism and CHD risk prediction based on clinical investigation among diabetes subjects. A total of 115 T2DM subjects were selected and divided into two groups, such as 78 T2DM subjects without Coronary Artery Disease (CAD) and 37 T2DM subjects with CAD. The ε3 allele being the most common in both groups. The findings revealed ε4 allele in T2DM subjects with CAD had higher LDL and HDL alleles. As a suggestion, the larger sample size should be carried out to verified the appearance of the ε4 allele as a risk factor of CAD among T2DM patients in Malaysia.

In Iran, a study by Vaisi-Raygani et al. (29) recruited 714 subjects. There were 152 T2DM subjects with CAD, 262 non T2DM subjects with CAD and 300 healthy subjects as control. The study showed T2DM subjects with the APOE ε2 and ε4 alleles acquired a greater chance of expanding CAD than non-diabetic subjects in Iran's western population. Besides, the ε4 allele becoming more intently linked with CAD compared to the ε2 allele.

Previous study by Chaudhary et al. (30) enrolled 149 healthy subjects as controls, 155 T2DM subjects without CAD and 147 T2DM subjects complicated with CAD as case-patients. They reported the ε4 allele as an independent risk factor in the correlation between subjects diagnosed with T2DM and CAD.

## CONCLUSION

The ε4 allele has been identified as an independent risk factor for both T2DM and CVD. This review also demonstrates the need for more research with larger sample size to establish association for APOE gene polymorphisms among patients with diabetes and CVD.

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