ORIGINAL ARTICLE

Apolipoprotein E gene and Disease Associated

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ABSTRACT

Metabolic syndrome is closely related to several disturbances in lipid and lipoprotein metabolism. Apolipoprotein E (apoE) e4 genotype prevalence varies among patients with metabolic syndrome by region and within each country. Further exploration is warranted to better understand the substantial heterogeneity of these prevalence estimates. This review attempts to highlight the probability of apolipoprotein E gene polymorphism as a risk factor for metabolic syndrome and/or coronary heart disease complications. An extensive literature review related to apoE, metabolic syndrome, and coronary heart disease was performed to describe related issues. This knowledge is a fundamental prerequisite for a possible diagnostic application of these lipoproteins as biomarkers to predict adverse cardio-vascular disease and metabolic syndrome.
Keywords: Apolipoprotein, metabolic syndrome, cardiovascular

INTRODUCTION

Polymorphisms in the ApoE gene may modulate lipoprotein metabolism at different steps, and influence total and low-density lipoprotein (LDL) cholesterol (LDLc) levels, as well as other lipid features. Population studies have documented significant differences in the frequency of apoE alleles related to the prevalence of various cardiovascular diseases. The ongoing population growth has led to a situation where cases of metabolic syndrome have concurrently expanded along the years. Most medical international expert groups agree that the syndrome is characterised by a cluster of conditions that occur together, such as abdominal obesity, dyslipidaemia, elevated blood pressure, glucose intolerance, and insulin resistance [1]. According to the American Heart Association (AHA), high blood pressure alone is a serious condition, but when a patient has high blood pressure along with high fasting glucose levels and abdominal obesity, this patient may be diagnosed with metabolic syndrome. There is a greater chance that this patient will have cardiovascular problems because of the combination of risk factors. Age, ethnicity, obesity, diabetes, and other diseases are also some of the risk factors that might increase the chances of having metabolic syndrome. Metabolic syndrome is closely linked to disturbances in lipid and glucose metabolism, which increase the risk of developing cardiovascular disease anddiabetes[1].

Approximately23%ofadultsareaffectedbymetabolicsyndrome,whichisclassified as a serious health condition, and they have a higher risk of contracting cardiovascular diseases, diabetes, stroke, and diseases related to fatty build-ups in artery walls. In 2000, 171 million people worldwide were affected by metabolic syndrome and this number is expected to increase to 366 million by 2030[2]. Although metabolic syndrome is a serious condition, the risks can be significantly mitigated by reducing weight, increasing physical activities, eating a heart-healthy diet that is rich in whole grains, fruits, vegetables, and fish, as well as working with health care providers to monitor and manage blood glucose, blood cholesterol, and blood pressure. Previous studies by Nazaimoon et al and Rampal et al reported that Malaysia has a higher prevalence of metabolic syndrome relative to other Asian countries[3,4]. Table 1 shows the prevalence of metabolic syndrome in Malaysia based on different diagnostic criteria, as reported by various investigators[5].

Table 1: Adult (Source: Ghee & Kooi, 2017)

Author	Sample size	Characteristics	Prevalence of Metabolic Syndrome by different criteria (%)				
			WHO	IDF	NCEP ATPIII 2001	NCEP ATP III 2005	Harmonised (JIS)
(Rampal et al., 2012)	18805	>15 years old Pen Malaysia and Sarawak		27.5			
(Tan et al.,2011)	2366	25–64 years old		30.1		36.1	
(Nazaimoon etal.2012)	4341	>18 years old Pen Malaysia and Sabah	32.1	37.1	34.3		42.5
(Moy and Bulgiba, 2010)	1494	University staff >35 years old Malays		38.2		41.4	
(Chu and Moy, 2013)	686	University staff >35 years old Malays				31.9	
(Heng et al., 2012)	227	University staff 20–65 years old Malays		38.8	33.5		38.3
(Tan et al., 2008)	109	Opportunistic contact 30–65 years old KL and Selangor	6.4	22.9	16.5		
(Zainuddin e tal., 2011)	298	Villagers 18–59 years old Kelantan		32.2	28.5		
(W. S. Tan et al., 2011)	1046	Men >40 years old Subang Jaya		31.6			
(Ramli et al., 2013)	8836	Urban and Rural >30 years old Pen Malaysia and Sabah		37.4	26.5		43.4
(Chee et al., 2014)	675	Government employees >20 years old Putrajay		46.3	27.9		48.9

Rampal et al summarised the prevalence of metabolic syndrome by age, gender, and ethnicity among Malaysians, as shown in Table 2. Numerous researchers have proven that the prevalence of metabolic syndrome increases with age and that females have a higher prevalence of metabolic syndrome. Indians, both men and women, have the highest rates of metabolic syndrome compared to other ethnic groups in Malaysia[4].

Table 2: Prevalence of Metabolic Syndrome by age, gender, and ethnicity among Malaysians ≥15 years old based on the IdF criteria in 2004 (Source: Rampal et al., 2012)

Prevalence (%)			
	Female	Male	Total
Age 15–40 years old Malays	15.7	14.7	15.2
Chinese Indians	13.9	13.4	13.7
Indigenous Sarawakians	23.3	21.8	22.5
	26.3	22.1	24.2
Age >40 years old	51.5	38.5	45.0
Malays Chinese Indians	45.4	36.3	40.8
Indigenous Sarawakians	64.9	51.3	58.3
	47.2	34.4	40.6

Apolipoprotien E and Lipid: Apolipoproteingene family consists of apoE gene, Apo(A- I),Apo(A-II), Apo(A-IV),Apo(C-1), Apo(C-II),andApo(C-III)(Chan,1989).There are four exons and three introns involving 3,597 nucleotides that encode 299 amino acid polypeptides in apoE gene[6]. The three common alleles are ε2, ε3, and ε4, with the ε3 allele being the most common. It can be found in more than 80% of the general population, followed by ε4 and ε2, and these alleles are located on chromosome 19[6]. These all elescode for three isoforms, which further determine the six genotypes as follows:ε2/ε2,ε4/ε2,ε3/ε2,ε3/ε3,ε4/ε3, and ε4/ε4[7].

The presence of apoE gene plays a major role in lipoprotein metabolism and lipid transport[8]. The apoE gene gives all the instructions and guidance in the process of making aprotein called apolipoprotein E. This protein then combines with fats (lipids) in the body to form molecules called lipoproteins. Lipoproteins are responsible for packaging cholesterol and other fats, and carrying them through the bloodstream. It is a must in maintaining normal levels of cholesterol in order to prevent disorders that affect the heart and blood vessels (cardiovascular diseases), including heart attack and stroke. ApoE, also known as a multifunctional protein, is found in all lipoproteins, except for low-density lipoprotein cholesterol (LDL-C), which plays a critical role in lipoprotein metabolism. Therefore, it is biologically possible forapoE toin fluence an individual's susceptibility to metabolic syndrome, especially in terms of both triglyceride and cholesterol levels, which are major complications of metabolic syndrome. The altered expression or genetic polymorphism of apoE is considered as a risk factor for metabolic syndrome. The possible association of apoE with the risk of metabolic syndrome has been widely investigated in different populations[9].

ApoE is synthesised and secreted by different organs and cells, including the brain, liver, kidneys, spleen, adrenals gonads, and macrophages[10]. It can also be found in abundance in plasma, interstitial fluid, and lymph nodes. ApoE is important for the plasma lipid levels, and in the regulation of plasma and tissue lipid content because apoE has a high binding affinity for lipoprotein receptors. However, each isoform of the apoE has different interactions with these receptors[11]. Differences in the structural and binding affinity of apo E, such as apo E2, apo E3, and apo E4 to the lipid are associated with the distribution of isoform-specific apoE among the different lipoproteins[12,13].Inthenervoussystem,neurons preferentially express the receptors for apoE, while non-neuronal cell types, most notably astroglia and microglia, are the primary producers of apoE.

Each apoE isoform also differs in binding affinity to cell surface heparan sulphate proteoglycans (HSPGs). Though the exact mechanisms remain to be elucidated, isoform 4 of apoE, encoded by anapo Eallele, has been associated with increased calcium ion levels and apoptosis following mechanical injury. The association of apoE with HSPG should attract and sequester apoE, which contain lipoproteins and assist their interaction with the low-density lipoprotein receptor (LRP). HSPGs interfere with the internationalisation of the apo E-containing lipoprotein[14]. The frequencies of the common polymorphisms at the apoE locus (ε2, ε3, and ε4) are different between populations, and can affect plasma lipids and cardiovascular disease in the population[15].Similar study by Bennet et al. conducted a research on apoE gene polymorphisms in various populations[16].

From a previous study, seven mammalian receptors for apoE were identified, which belong to the evolutionarily conserved LRP family[17]. ApoE was initially recognised for its importance in lipoprotein metabolism and cardiovascular disease. ApoE deficiencies may result in familial dysbetalipoproteinemia or also known as type III hyperlipoproteinemia (HLP III), in which elevated plasma cholesterol and triglycerides are the consequence of impaired clearance of chylomicron, VLDL,and LDL [12].

Apolipoprotien E Polymorphism and Its Associated Disease: Cardiovascular disease (CVD) is a chronic condition, and the world's most significant cause of death and morbidity. The exact aetiology of CVD remains questionable. Nonetheless, some ecological and genetic components that can increase CVD risk are known. Factors, such as cigarette smoking, physical inactivity, and alcohol consumption, as well as the consumption of dietary fat, especially the soaked saturated fats, are considered as the main risk factors for CVD. Some vulnerability qualities have recently been suggested to demonstrate their relationship with CVD. Regular polymorphism in the apoE gene is one of the genetic determinants that have receiveda lot of attentionbecauseit corresponds to the risk of CVD[16.18].

CVD, similar to coronary heart disease, refers to any confusion that essentially leads to Coronary Artery Disease (CAD), Vascular Disease (VD) of the brain and kidney, and peripheral arterial disease in the cardiovascular environment. The organic behaviour of apoE can be determined by changes in its structure and quantity. Epidemiological analyses have shown the distinctive relationship between apoE and CVD, and their effects on cholesterol levels. An analysis among middle-aged men found that 40% of the E4 transporter population had such a high risk of CVD mortality compared to those with the genotypes E3/E3 or E2 [19].

Previous studies have shown that there is an increased risk of death from CVD among E4 carriers [20,21]. Some analyses have linked the E4 allele to an increased risk of coronary arterial disease and localised myocardial necrosis. In Finland, Scotland, and Northern Ireland, the highest recurrence of E4 allele was associated with higher cholesterol levels and higher CVD mortality rates. In addition, an increased risk of CVD has also been linked to

the E2 allele [19]. Examination of the recurrence of the apoE genotype and the associated CVD has revealed that Indians, Asians, and Mexican Americans showed the most notable E3 recurrence (84%). The highest E4 level was recorded by Africans and African-Americans at 20.1% and 31%,respectively. The highest E2 level was reported by African-Americans and Caucasians, except the Finns (7.3%–13.1%)[22]. So far, some studies have shown that the apoE E4 allele is a risk allele for CVD, although others have not found a connection. The duplication of apoE remains complicated and requires further analysis to determine its specific capacity in causing cardiovascular and cerebrovascular disorders.

Type III hyperlipoproteinemia (HLP), commonly known as dysbetalipoproteinemia or broad-beta disease, is an inherited disorder that is described by persistent testimony of plasma lipoproteins and premature atherosclerosis[23]. Type III HLP results from the aggregation of chylomicron accumulation from intestinal lipoproteins and VLDL deposits derived from liver lipoproteins. The declaration of various apoE isoforms, which may not be receptor-bound and apoE deficiency, was associated with the HLP of type III arrangement[24]. The presence of apoE2 was also associated with the essential atomic ratio for type III HLP. ApoE E2 increases triglyceride and cholesterol rates, which will lead to a change in lipoprotein-free hepatic and intestinal residues, and contributes to type III HLP structure. Hyperlipidaemia is caused by the inheritance of two apoE E2 alleles, and most allele transporters are normolipidemic or hypocholesterolaemic. Some analyses have shown that type III HLP can occur with a recurrence of 1 to 5 per 5,000 people. Type III HLP also occurs among the Caucasian populations with a relapse of 0.5–1.0 per 100 people having E2 / E2 homozygous. More than 90% of patients with type III HLP are homozygosity for the E2 / E2 allele (Arg158 → Cys), and it is well known amultifactorial gene that was acquired passively[25]. A series of notable, normally occurring apoE changes were also characterised, corresponding to the predominant inherited mode of type III HLP at an early age[15].

T2DM is also a ubiquitous category that affects 90% of diabetes mellitus cases. T2DM has affected almost 4% of the world population and could grow to 5.4% by 2025[26]. A mixture of lifestyle and genetic variables could cause further development of T2DM[27]. Studies have recently shown that more established T2DM patients are at an increased risk of mental impairment or dementia. T2DM is also associated with clinical analysis of dementia of the Alzheimer's disorder (AD) type, not exclusively vascular dementia (VD)[28].

ApoE performs an important function in the control of plasma and cellular lipid groups 37, and the apoE isoforms could represent strains with synthetic stability[29]. The apoE polymorphism could be one of the variables that affect the formation of T2DM. Some analyses have shown that a huge risk of T2DM is related to the ApoE2 allele[30].

A meta-analysis of 29 analyses, which included 4,615 cases of T2DM and 2,867 controls among the Han Chinese population recommended that the apoE E2 and E4 alleles could be associated with higher casesof T2DM and diabetic nephropathy[31]. Additionally, some analyses have shown that the risk of T2DM is related to apoE E4. Similarly, mental deficiencies were only found in people with T2DM and an apoE E4 allele [32]. The relationship between T2DM and AD between transporters of the apoE E4 allele was particularly strong. T2DM is related with a decrease in intellectual capacity and dementia-like AD.

CONCLUSION

To the best of our knowledge, no dedicated consensus is available on the criteria of metabolic syndrome that is best suitedforourpopulationinordertoallowbetterdataanalysisand mergers.Further studies should be conducted to evaluate the association of APOE gene and its risk factors. Due to the growing rate of metabolic syndrome, more research should investigate effective management programmes that could help us tackle the problem of metabolic syndrome better. The differences in human population may also influence the association of Apo E genepolymorphism and metabolic syndrome. Therefore, it is essential to conduct an extensive study that can provide a solid explanation on this genetic variation and its impact on the possibility of developing metabolic syndrome.

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