International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 5 Sep-Oct 2022, pp: 171-174 www.ijprajournal.com ISSN: 2456-4494

Clinical Correlations of Apolipoprotein E Polymorphism

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Submitted: 05-09-2022 Accepted: 13-09-2022

Highlights:
The study of the biological significance of the Apo E polymorphism in patients with diabetes is important for pathogenesis of hyperlipidemia and atherosclerosis.

Abstract: Studies conducted so far show controversial results, which suggests that both low and high levels of Apo E and its genotypes, respectively E2, E3 and E4 alleles influence the progression of renal nephropathy in diabetic patients but also with interest of the cardiovascular and nervous system.

Keywords: Apolipoprotein E, atherosclerosis, genetic polymorphism, diabetes

I. INTRODUCTION:

Apolipoprotein E (Apo E) is a glycoprotein, 34Kda, produced mainly in the liver, but which can also be produced locally in the brain, kidneys, spleen and macrophages. It is a component of all classes of lipoproteins except LDL. Apo E acts as a ligand for chylomicron receptors and VLDL remaining in the liver, and is involved in the transport of cholesterol as a component of HDL (1, 2, 3).

The protective role of Apo E in the development of atherosclerosis has been demonstrated for the first time in animals. Other research studies have shown that Apo E is an anti-atherogenic protein in human studies. It has also been shown that cholesterol-laden macrophages show a higher expression of the Apo E gene. Apo E deficiency in these cells leads to increased cholesterol efflux and the formation of atheromatous plaque (7, 8).

There are 3 common isoforms of Apo E (Apo E2, Apo E3, Apo E4) encoded by three alleles (ε 2, ε 3, ε 4) on chromosome 19q13.2. Due to the differences in the structure of Apo E isoforms, they have different binding capacity, as well as lipoprotein binding preferences, which leads to a varied influence on lipoprotein metabolism. The Apo E3 and Apo E4 isoforms bind to the LDL receptor with a similar affinity, while Apo E2's interaction with the receptor is only at 2% of normal activity. The Apo E2 and Apo E3 isoforms bind preferentially to HDL, while Apo E4 binds to large triglyceride particles (VLDL). Apo E3 is the most common isoform (approximately 77% of the Caucasian population), and does not affect lipoprotein metabolism. Apo E4 occurs in 15% of the population, and can lead to an increased concentration of LDL cholesterol. Apo E2 is the rarest isoform (8%), and could be correlated with hypertriglyceridemia. Disorders at this level can contribute to the acceleration of atherosclerosis. The genetic polymorphism of Apo E also influences the concentration of Apo E in serum; the highest levels were found in ε 2 allele carriers, and the lowest in ε 4 allele carriers (9, 10, 11).

Numerous studies have shown that patients with cardiovascular disease have elevated concentrations of Apo E, but the researchers pointed out that the distribution of Apo E in lipoproteins plays a major role in the overall plasma concentration of Apo E, and is not an ideal parameter to assess cardiovascular risk. The genetic polymorphism of Apo E can influence the metabolism of lipids and lipoproteins (12, 13, 14,15).

Wang Y. et al. have shown that carriers of the E4 allele who underwent haemodialysis have elevated levels of cholesterol, triglycerides and LDL cholesterol. Chronic kidney disease is one of the most common diseases worldwide, due to its increasing frequency, complications and mortality due to accelerated atherosclerosis. The leading cause of death in this population is cardiovascular

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disease correlated with dyslipidaemia, which is observed in the early stages of renal failure associated with a decrease in glomerular filtration rate. Hypertriglyceridemia and disorders in lipoprotein metabolism have been well defined in cardiovascular disease (4, 5, 6).

Some studies have indicated cholesterol as a key component of atheromatous plaque in the arteries, hence the hypothesis of the pathogenesis of atherosclerosis. Studies in the population have shown that elevated levels of LDL cholesterol and apolipoprotein B (Apo B 100), the main protein structure of LDL, are directly associated with the risk of atherosclerosis and cardiovascular events. Arterial lesions cause endothelial dysfunctions that modify Apo B containing lipoproteins, and the infiltration of monocytes into the subendothelial space. Macrophage inflammation results in oxidative stress and cytokine/chemokine secretion, causing LDL oxidation, endothelial cell activation and atheromatous plaque formation. HDL, Apo A-I and endogenous Apo E prevent inflammation and oxidative stress, but also stimulate cholesterol outflow to reduce the formation of lesions. The coexistence of diabetes mellitus and other factors, particularly dyslipidaemia, further increases the risk of cardiovascular death. A characteristic pattern, called diabetic dyslipidaemia, consists of elevated triglyceride levels, low HDL levels and postprandial lipemia, and is common in patients with type 2 diabetes mellitus or metabolic syndrome (16, 17, 18,19,25).

Depression is a serious mental disorder that affects human health, characterised by emotional dysfunction. The World Health Organization speculates that by 2020, depression will become the main reason why individuals will not be able to work. The incidence rate of depression has increased in recent years. The current prevalence of depression is 3-5%, which is the second largest economic burden of the disease. The relationship between the genetic model and susceptibility to depression has been investigated based on family studies. A meta-analysis of seven studies showed that the impact of hereditary depression accounted for 37% of cases, while environmental factors accounted for 63%. New discoveries in molecular biology and biotechnology have created new opportunities in detecting alleles susceptible to increased risk of depression. Apolipoprotein E with the 3 alleles included, ε 2, ε 3 and ε 4, may be genes susceptible to depression. Some researchers, Wand W. et al., have reported that the genetic polymorphism of Apo E is a risk factor for triggering depression. The frequency of alleles ε2, ε3 and ε4 was 5.3%, 88.4% and 6.3%, respectively, in humans, and the frequency of ε4 was the lowest in all ethnic groups. After completing the meta-analysis study, the abovementioned researchers concluded that the Apo E ε4 allele may be associated with depression and may determine the severity of depression (20, 21, 22).

Apo ε4 is associated with familial Alzheimer's disease with late onset. There is an increased affinity and specific binding between the beta-amyloid peptide and ApoE. One study suggests that non-lipidic bonds, such as cellular mechanisms for remodelling in kidneys, may be involved in the association of ApoE alleles and the progression of chronic kidney disease. ApoE genotypes shape lipoprotein metabolism differently, are expressed in the kidneys, and differ in frequency depending on race. Also, ApoE isoforms may have specific effects on the smooth muscles of the vessels as well as in the proliferation of mesangial cells, which may affect the progression of chronic kidney disease. ApoE predicts the progression of the chronic kidney disease, independent of diabetes, race, plasma lipid values and non-lipid risk factors (20, 21).

The association of Apo E phenotypes with other forms of hyperlipidaemia is described in a New Zealand study. The increased frequency of the ε2 allele was associated with hypertriglyceridemia but also an increased prevalence for the other alleles, namely ε3 and ε4. This frequency was observed both in patients with hypertriglyceridemia, mixed hyperlipemia (elevated cholesterol and triglycerides), and in those with hyperlipidaemia associated with diabetes mellitus. Several studies have reported a link between Apo E polymorphism and the occurrence of cerebral haemorrhage, but the findings remain controversial. Numerous meta-analyses have concluded that there is a close link between ethnicity and Apo E polymorphism. The ε3 and ε4 alleles were compared, and a significant increase in the ε4 genotype was found in patients with cerebral haemorrhage. These indicate that the ε4 allele is a risk factor for cerebral haemorrhage, for the white population, but not for the black population. Apo E has been reported to be associated with countless diseases of the nervous system. In addition to cerebrovascular disease, ε4 dosage is a risk factor for the early onset of Alzheimer's disease, and in these families, ε4 is sufficient to cause this disease until the age of 80; it has also been reported that ε2

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alleles have a protective effect in sporadic Alzheimer's disease. Apo E has an impact on human cognitive function, ε4 having a significantly increased frequency in ischemic stroke patients, and is an independent risk factor for ischemic stroke and cardiovascular disease (22, 23, 24).

II. MATERIALS AND METHODS:

We searched the Pubmed databased from March 1st 2015 using the key words "apolipoprotein E polymorphism", "atherosclerosis", "diabetes", "lipoprotein metabolism" and "alleles". Only articles written in English were evaluated.

III. RESULTS:

Apolipoprotein E has a role beyond lipoprotein metabolism. Correlation of Apo E4 allele is present in cardiovascular, neurological and infectious diseases compared to Apo E2 and Apo E3. Studies of the structure of Apo E2 show that it has a major deficiency in LDL binding receptors, due to the structure that alters these receptors known to be a part of the mechanism in grade III hyperlipoproteinemia.

Apo E4 is the major genetic factor for Alzheimer's disease and determines the stage of the neuropathological disorder due to genetic and metabolic environmental stressors. Apo E it also influences susceptibility to parasitic, bacterial and viral infections. In HIV positive patients, Apo E4 homozygosity shows progression to AIDS and increasing susceptibility to opportunistic infections.

IV. CONCLUSIONS:

Apolipoprotein E is known for its ability to suppress atherosclerosis. Besides its activity to remove the remaining lipoproteins from plasma, Apo E is also known for its direct influence on the numerous cells of the vascular walls, immune system and bone marrow. Apolipoprotein (Apo) E plasma, is a key factor of lipid metabolism. Most of the circulating ApoE is of hepatic origin, but can also be synthesized in the spleen, kidneys, lungs, muscle and central nervous system . The clear, detailed definition of ApoE function in the 3 target locations, the hypothalamus, adipose tissue and plasma, can lead to an effective screening method based on the determination of the plasma lipid profile, ApoE becoming a readily detectable marker of metabolic disorder.

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