Research Article

A study of Apo lipoprotein 'E' polymorphism and lipid profile in coronary artery disease

S. M. Mallakmir[1*], G. R. Kane[1], S. S. Mallakmir[2], D. A. Vidhate[3], S. Deshpande[1], J. Nadkarni[4], M. David [4], G. Ravindranathan[4], J. Shah[4]

[1]Department of Cardiology, [2]Clinical Geneticist, [3]Department of Biochemistry, Pad. Dr. D.Y. Patil Medical College and Research centre, Nerul, Navi Mumbai, INDIA.
[4]Department of Biotechnology and Bioinformatics, CBD Belapur, Navi Mumbai, INDIA.
Email: drmsomnath@gmail.com

Abstract

Apo lipoprotein E (Apo E), a glycoprotein, plays an important role in lipoprotein metabolism. Polymorphism in Apo E genotype affects the clearance of circulatory lipids and leads to dyslipidemia. Association between Apo E polymorphism and risk of coronary artery disease (CAD) has been evident in earlier studies, but its significance has not yet been established. Indian literature in this subject is scant and cultural, ethnic diversity in Indian population can influence the results, hence there is need for more studies in different population groups. We have studied 160 cases during 2009 to 2012, referred to the Department of Cardiology, Dr. D.Y. Patil Hospital and research Centre, Nerul, Navi Mumbai. Lipid profile and Apo E polymorphisms (E2/E3, E3/E3 and E3/E4) were studied in 110 CAD patients and compared them with 50 healthy controls. **Conclusions:** Our results reported that Apo E3/E4 genotype is one of the most potent genotype associated CAD with abnormal lipid profile.

Keywords: Apo lipoprotein E polymorphism, coronary artery disease and Lipid profile

[*]**Address for Correspondence**
Dr. S.M. Mallakmir, Department of Cardiology, Pad. Dr. D.Y. Patil Medical College and Research centre, Nerul, Navi Mumbai, INDIA.
Email: drmsomnath@gmail.com

Received Date: 01/06/2014 Accepted Date: 10/06/2014

Access this article online

Quick Response Code:

Website: www.statperson.com

DOI: 11 June 2014

INTRODUCTION

Coronary artery disease is the leading cause of death worldwide and is rapidly increasing in prevalence in developing countries[1]. CAD has been associated with behavioral, genetic and environmental risk factors[2]. Amongst genetic risk factors, Apo E is one of the most thoroughly studied genetic polymorphisms particularly for its effect on lipid profiles and CAD risk[3].India is facing a great challenge because of enormous increase in CAD cases in last few years.Indian literature in this subject is scant and cultural, ethnic diversity in Indian population can influence the results, hence there is need for more studies in Indian population. Plasma lipoproteins are composed of nonpolar lipid core, primarily triglycerides and cholesteryl esters with an external layer of phospholipids and Apo lipoproteins. Apo lipoproteins are the only protein components of lipoproteins which combine with free cholesterol, phospholipids, cholesterol esters and triglycerols to form lipoprotein. Like the different types apolipoprotein, apo E helps to stabilize as well as required for clearance of lipoproteins. Apo E is critical in the metabolism of very low density lipoproteins (VLDL) and chylomicrons [4].The structural gene locus for this lipoprotein is at chromosome 19 q 13.2[5]. And consists of four exons and three introns spanning 3.597 nucleotides and produces a 299 amino acid polypeptide with a molecular mass of about 34 k Da, three common all else designated E2, E3 and E4 code at a single locus. The various Apo E is o forms interact differently with specific lipoprotein receptors ultimately altering circulating levels of triglycerides and cholesterol. Apo E binds to specific receptor cells in liver but there is functional difference between Apo E alleles. While Apo E4 and E3 bind with approximately equal affinity to lipoprotein receptors, Apo E2 binds with less than 2% of this strength, the difference in uptake of postprandial lipoprotein particles contributes to the genotypic differences in total and LDL cholesterol levels [6]. A strong

How to site this article: S. M. Mallakmir *et al.* A study of Apo lipoprotein 'E' polymorphism and lipid profile in coronary artery disease. *International Journal of Recent Trends in Science and Technology* June 2014; 11(2): 234-237 http://www.statperson.com (accessed 13 June 2014).

correlation was observed between Apo E polymorphism, circulating LDL and Apo B-100 which may enhance atherogenesis by affecting their circulating levels. Blood lipids and lipoproteins are the major coronary risk factors and hence Apo E polymorphism has been studied in greater details in last few years[7].

AIM

Our aim is to investigate the association of Apo E polymorphism and Lipid profile in CAD patients defined by coronary angiography.

METHODOLOGY

We studied total 160 subjects. Out of which 110 CAD patients were from Indoor patient department (IPD) and 50 normal controls visiting Outpatient department (OPD) of Cardiology department, Pad. Dr. D. Y. Patil Hospital and research center, Nerul, Navi Mumbai, during the period of 3 years. The CAD was diagnosed on basis of clinical symptoms and signs, electrocardiography (ECG) and echocardiography and coronary angiogram (CAG). Lipid profile was assessed and Apo E polymorphism was evaluated in all study participants. Written informed consent was obtained from each participant before inclusion in the study. This study was approved by the University ethical committee. Fasting blood samples were collected from all the study participants. Triglyceride, Total cholesterol (TC), LDL cholesterol, HDL cholesterol and VLDL levels were measured by auto analyzer. Fasting venous blood collected in EDTA sample tube for the detection of Apo E genotypes.DNA extraction was carried out by using Qi Amp Blood Mini Kit. Extracted DNA samples were checked for quality and quantity analysis. DNA was amplified by PCR in a thermal cycler using specially designed oligonucleotide primers (8). Restriction enzyme digestion of the amplification products was carried out. Finally separation of the digested products and identification of genotype was done by agarose gel electrophoresis. Data is presented as mean and standard deviation (S.D.). SPSS version 16.0 statistical package was used to analyze the data. Independent test was applied to determine the statistical significance of the variable in the study groups.

RESULTS

Table 1: Demographic Data

Variables		CAD (110)	Normal (50)
AGE	>45 (85)	27.3%	90.0%
	<45 (75)	72.7%	10.0%
Sex	M(118)	76.4%	68.0%
	F (42)	23.8%	32.0%
HT (88)		80.0%	0%
DM (56)		50.9	0%
NICOTINE (79)		71.8%	0%
ALCOHOLIC (15)		13.6%	.0%

The study data revealed that 27% CAD patients and 90 % controls were below age of 45 and 72.7 % CAD cases and 10 % controls were above age of 45. Gender wise (M/F) ratio in the present study is CAD (4:1) and control (3:1). In CAD group 80% patients were hypertensive, 50.9% were Diabetic. It was observed that in CAD group 71.8% subjects were consuming nicotine in any form while 13.6% subjects were alcoholic.

Table 2: CAD and lipid profile

Variables	CAD (110) Mean	Normal(50) Mean ± S.D.	'p' value
TC	209.95(±)29.50	166(±)34.68	.000
HDL	37.79(±)6.57	46.08(±)9.01	.000
TAG	182.30(±)45.85	142.44(±)102.58	.000
LDL	135.43(±)25.79	92.8(±)25.79	.000
VLDL	36.43(±)9.24	27.24(±)16.82	.000
Non HDL chole	172.68(±)28.89	121.24(±)36.27	.000
TC/HDL	5.62(±)1.21	3.67(±)0.95	.006
LDL/HDL	3.66(±)0.99	2.07(±)0.66	.000

The present study observed a significant difference in lipid profile of CAD and normal controls. Circulatory levels of various parameters of lipid profile showed a significant variations as Total Cholesterol (209.95±29.50/166±34.68), HDL (37.79±6.57/46.08±9.01), Triglycerides (182.30±45.85/142.44±102.58), LDL (135.43±25.79/92.8 (±) 25.79), VLDL (36.43±9.24/27.24±16.82), NonHDLChol (172.68±28.89/121.24±36.27), TC/HDL (5.62±1.21/3.67± 0.95) and LDL/HDL (3.66±0.99/2.07± 0.66) between CAD and control group.

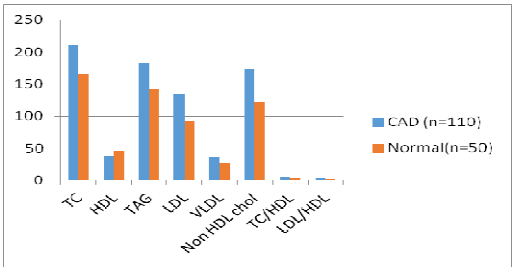

Figure1: Comparison of lipid profile parameters in CAD and Control groups

Table 3: Distribution of Apo genotype among CAD and normal controls

Apo E Genotypes	CAD (n=110)	Normal (n=50)
E2/E3(3)	2.7%	.0%
E3/E3(77)	70.0%	92.0%
E3/E4(30)	27.3%	8.0%

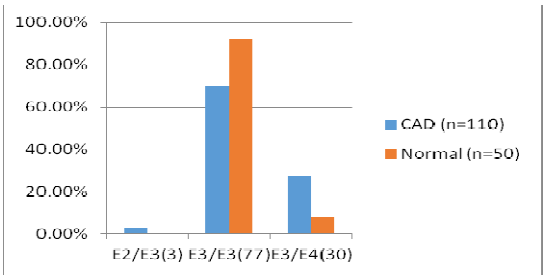

Figure 2: Apo E genotype distribution in CAD and Control

In our study E3/E3 is more frequent genotype [in CAD 70% and in control group 92%]. E3/E4 is genotype is mainly associated with CAD [in CAD (27.3 %) as compared to control group (in control group (8.0%)] which is statistically significant (P= 0.008). E2/E3 is less frequent genotype found in our study and also less frequently associated with CAD [CAD group (2.7%) and control group (0%)].

DISCUSSION

In this study we found a significant correlation between various parameters of Lipid profile between CAD patients and healthy normal controls. Further distribution of Apo genotype among CAD and normal controls was evaluated in all study participants. It was observed that E3/E3 is the more frequent genotype in both CAD and normal population. A study carried out by Aceves *et al*, included various populations and showed that E3/E3 is more frequent genotype as compared to E3/E2 and E3/E4 among different populations[9].while in 2011, Belkovets *et al*, studied Apo E genotypes in Siberian females[10]. Then in addition to that, E3/E4 genotype has been found to be associated more with CAD than controls. Our observations were supported by a study carried out by Singh *et al*, 2008[11]. While it was also observed that E2/E3genotype is less frequently associated with CAD. Apo E polymorphism E3/E4 influences lipoprotein metabolism which reflects in abnormal lipid profile and confer the risk of CAD. Apo E determines the clearance of VLDL[12] but due to specific polymorphisms, amino acid sequence in Apo E is disturbed which affects the structure of the Apo E protein and ultimately affects lipid clearance from the circulation[13]. The various Apo E iso forms interact differently with specific receptor, ultimately altering circulating levels of cholesterol. Apo E form VLDL, chylomicrons and chylomicrons remnants. Chylomicron remnants bind to specific receptor cell in the liver. Apo E2 is associated with decreased ability to bind the LDL receptor, hence less efficient at making and transferring VLDLs and chylomicrons from blood plasma to the liver. By contras carriers of E3 and E4 are much more efficient in this process. While Apo E3 A and Apo E4 binds with approximately equal affinity to LDL receptor, Apo E2 binds with less than 2% of this strength. Thus compared with carrier of E3or E4 alleles, carriers of E2 are slower to clear dietary fat from blood. The difference in uptake of postprandial lipoproteins particles result in difference in regulating hepatic LDL receptor which in turn contributes to genotypic difference in total and LDL cholesterol levels[14, 15.]

CONCLUSION

The study result concludes that Apo E3/E4 genotype is one of the most potent genotype associated with CAD due to abnormal lipoprotein metabolism. More cohort studies in India will help in genotyping this entity which will further impact preventive measures.

ACKNOWLEDGEMENT

We express our sincere gratitude to all teaching and technical staff members of Department of Cardiology and Medicine, Dr. D.Y. Patil Medical College, Nerul Navi Mumbai. We would also like to thank the teaching and technical staff of Department of Biotech and Bioinformatics, Dr. D.Y. Patil University, CBD, Navi Mumbai.

DISCLOSURE

No conflicts of interest are declared by the authors.

REFERENCES

1. Murray CJ, Lopez AD. The Global Burden of Disease: A Comprehensive Assessment of Mortality and Disability from Disease, Injuries and Risk Factors in 1990 and Projected to 2020. Boston, USA: Harvard University Press; 1996.
2. Scheuner MT. Clinical application of genetic risk assessment strategies for coronary artery disease: genotypes, phenotypes, and family history. Prim Care Clin Office Pract31 (2004) 711–737.
3. Bhanushali A and Das B. Genetic variants at the APOE, lipoprotein lipase (LpL), cholesteryl ester transfer protein (CETP) and endothelial nitric oxide (eNOS) genes and coronary artery disease (CAD): CETP Taq1 B2B2 associates with lower risk of CADin Asian Indians. J Community Genet 2010; 1:55–62.
4. Mahley RW, Innerarity TL, Rall SC, Jr, Weisgraber KH. Plasma lipoproteins: apolipoprotein structure and function. J Lipid Res. 1984; 25:1277–1294.
5. Dimitrios N Tziakas and Georgios K Chalikias. Role of apolipoprotein E genotype in Coronary artery disease. Future Cardiol. 2007; 3(5), 537–551.
6. Mahley, R. Apolipoprotein E: Cholesterol Transport Protein with Expanding role in Cell Biology *Science*1988;240: 622-640
7. Chaudhary R, Likidlilid A, Thavatchai Peerapatdit, Damras Tresukosol, Sorachai Srisuma Apolipoprotein E gene polymorphism: effects on plasma lipids and risk of type 2 diabetes and coronary artery disease. Cardiovascular Diabetology 2012, 11:36.

8. Emi M, Wu L L, Robertson MA, Myers RL, Hegle RA, White RR. Genotyping and sequence analysis of apolipoprotein E isoform. Genomics 1988; 3: 373.
9. Aceves D, Ruiz B, Nuño P, Roman S, Zepeda E, Panduro A. Heterogeneity of apolipoprotein E polymorphism in different Mexican populations. Hum Biol. 2006; 78(1):65-75.
10. Belkovets A. S, Kurilovich M, Dolgich and D.P**.** Agarwal. Distribution of Apolipoprotein E (APOE) Genotypes in a Siberian Female Population Sample. IJHG 2011 (3): 179-182.
11. Singh P, Singh M, Bhatnagar, D. Kaur, T.Gaur S. Indian Journal of Medical Sciences Mar 2008: 105-12.
12. Knouff C, Hinsdale ME, Mezdour H, Altenburg MK, Watanabe M, Quarfordt SH, Sullivan PM, Maeda N.Apo E structure determines VLDL clearance and atherosclerosis risk in mice. J Clin Invest. 1999; 103 (11): 1579-86.
13. Davignon J, Gregg RE, Sing CF. Apolipoprotein E polymorphism and atherosclerosis. Arteriosclerosis 1988(8):1–21.
14. Sing CF, Davignon J. Role of the apolipoprotein E polymorphismin determining normal plasma lipid and lipoprotein variation. Am J Hum Genet 1985; 37:268–85.
15. Weisgraber KH, Innerarity TL, Mahley RW "Abnormal lipoprotein receptor-binding activity of the human E apoprotein due to cysteine-arginine interchange at a single site". *J. Biol. Chem.1982;* 257(5): 2518–21.

Source of Support: None Declared
Conflict of Interest: None Declared

