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Postprandial Lipemia, Genetics and CHD Risk

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New biochemical and genetic markers will be required to be more successful in the prevention of coronary heart disease. Postprandial lipid metabolism has received considerable attention since it was shown that postprandial triglyceride-rich lipoproteins are independently involved in the development of atherosclerosis. Multiple genes and environmental factors work in concert to alter these lipid. In this paper, postprandial lipemia, genetic variation and cardiovascular risk will be reviewed.

Key words : postprandial lipemia, genetics, coronary heart disease(CHD)

INTRODUCTION

CHD remains the leading cause of death and disability in our society. In the U.S., approximately 500,000 deaths per year are due to this disease and this number is at the global level 7.2 million, and as many women die from this disease as do men. Because about half of all deaths from heart disease are sudden and unexpected, there is little opportunity for treatment. For people at risk of sudden death, prevention is their best hope. Atherosclerosis begins in young adulthood, but it may be decades before manifestation of clinical disease. We do not fully understand all the causes of heart disease, but large epidemiological studies have identified risk factors and strategies to reduce the risk.

CHD risk factors & CHD prevention

Major non modifiable CHD risk factors include age, gender and family history of premature CHD. However, there are other risk factors we can change, treat or modify and these include: cigarette and smoking, high LDL-C, low HDL-C, high blood pressure, physical inactivity, obesity and overweight, and diabetes mellitus.

The recent age adjusted decline in death rates from cardiovascular disease in the United States is due largely to the public's adopting a more healthful lifestyle. This underscores why it is important for the medical profession to advocate prevention strategies. More and more evidence shows that atherosclerotic plaques in arteries can regress even in people with advanced disease. As our understanding of the causes of heart disease improves, the day will come when we can direct preventive measures at the disease process itself.

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The opportunity to reduce the major causes of morbidity and mortality from CHD is at hand. By focusing on prevention, we can have a major impact on people's health. This is especially true for CHD because of the wealth of knowledge about how to help prevent it. In the long run, it makes sense that prevention costs less than expensive interventions. However, the knowledge of all the classical risk factors does not provide yet enough precision to determine future individual risk of developing CHD. Therefore, new biochemical and genetic markers will be required to achieve better precision and to be more successful in the prevention of CHD. At this regard, we should keep in mind that, in affluent countries, humans are mainly in the postprandial state. Considering that the gastrointestinal system is busy with the processing of an ingested meal for at least 6-8 hours and if the average person takes three meals per day, the conclusion is that for most of the 24 hours of a day the intestine is working. The digestive system works efficiently and dynamically with dietary fat, with virtually none being excreted (<5%). This places the gut as a central organ in lipid metabolism, even above the liver, and underlines the importance of postprandial lipemia.

Postprandial lipemia

Postprandial lipid metabolism has received considerable attention since it was shown that postprandial triglyceride-rich lipoproteins (TRL) are involved in the development of atherosclerosis.[1),2)] Studies comparing CHD patients and controls have demonstrated differences in postprandial TG after an OFLT[3)] and that the postprandial TGs are an independent predictor of CHD in multivariate analysis.[2)] A delayed clearance of retinyl palmitate (RP), used to study the metabolism of TRL of intestinal origin, discriminates between CHD patients

and controls,[4] after adjusting for fasting TG or HDL-C in normolipidemic men.[5] The relation of postprandial lipids to atherosclerosis makes this evaluation a priority in atherosclerosis research. It is no longer possible to ignore its importance and to try to explain the relation between lipids and atherosclerosis exclusively on the basis of the fasting lipid levels. Indeed the fasting lipid level may be stable, but is a relatively artificial physiological parameter. In the future not only diagnosis, but also treatment of hyperlipidemia with the aim to reduce atherogenesis should be geared as much towards postprandial lipids and their biochemical and genetic determinants as to fasting lipids. This is especially important in view of the alarming upward trend observed in recent years in diabetes mellitus, a major risk factor for CHD. Diabetes cases in adults will more than double globally from 143 million in 1997 to 300 million by 2025 largely because of population ageing, unhealthy diets, obesity and a sedentary lifestyle. It has been shown that increased postprandial lipemia is an inherent feature of diabetic dyslipidemia. However, the ephemeral character of postprandial lipid metabolism, the dynamic nature of changes in blood lipid levels and the problem of separating intestinal from hepatic particles, all have made the evaluation of postprandial lipoprotein metabolism difficult.

Gene relationship to postprandial lipemia

To understand the etiology of CHD better, researchers have examined the relative contribution of genetic and environmental influences on some of its major risk factors and specifically on plasma lipid and lipoprotein levels. The outcome of these studies has been highly variable, and the genetic effects reported range from 0.19 to 0.80 for TG, 0.42 to 0.70 for TC, 0.40 to 0.68 for LDL-C, 0.36 to 0.62 for HDL-C and up to 0.98 for Lipoprotein(a) [Lp(a)]. This approach, although highly informative, does not usually provide information about specific gene(s) responsible for the observed heritability. During the decade of the eighties, the genes for many of the known proteins involved in lipoprotein metabolism were cloned and characterized. Genetic variability at these loci was used to examine associations between these genes, plasma lipid levels and ultimately CHD risk. The results of the initial studies were mixed. This was in part due to the fact that most studies suffered from lack of statistical power, and conclusions were drawn from sample sizes that were too small. However, it should be recognized that the techniques available during the early eighties were not optimal to carry out large population studies. Another deficiency detected in most studies was the lack of inclusion of environmental factors in the analysis. This is especially important when examining phenotypes, such as lipids, influenced by so many factors. Nowadays, the polymerase chain reaction (PCR) has made it possible to carry out genetic studies on larger sample sizes. Moreover, the increase in sample size has allowed a more careful examination of the interaction between genetic and environmental factors, especially nutritional factors. Therefore, we are beginning to get some understanding of the genetic factors that modulate the variability in response of fasting lipid levels

Table 1. Summary of the gene variants which may be associated with individual variability in postprandial lipemia

Locus	Chromosomal location	Polymorphism	Position	Type of variation	Reported frequency
APOA1	11q23.1-11q23.2	-75G/A	5' flanking region	G/a	0.80/0.20
APOA4	11q23.1-11q23.2	T347S	Exon 3	A/t	0.78/0.22
		Q360H	Exon 3	G/t	0.88/0.12
APOB	2p24-2p23	AA12ins/del	Exon 1	+/- 3 amino acids C/t	0.63/0.37
		T2488T (XbaI)	Exon 26		0.53/0.47
APOC3	11q23.1-11q23.2	C3238G (SstI)	3' UTR	C/g	0.92/0.08
APOE	19q13.2-19q13.2	E2 : Cys112Arg	Exon 4	T/c	0.08
		E3	Exon 4		0.79
		E4 : Arg158Cys	Exon 4	C/t	0.13
CETP	16q13-16q13	G+279/in1A(TaqIB)	intron 1	G/a	0.58/0.42
CYP7	8q11-8q12	A-204→C	5'flanking region	C/a	0.59/0.41
FABP2	4q28-4q31	Ala54→Thr	Exon 1	G/a	0.71/0.29
LIPC	15q21-15q22	C-514→T	5'flanking region	C/t	0.79/0.21
LPL	8p22-8p22	D9N	Exon 1	G/a	0.97/0.03
		N291S	Exon 6	A/g	0.97/0.03
		Ser447X	Exon 9	C/a	0.83/0.17
SRBI	12q24	Gly2Ser	Exon 1	G/a	0.88/0.12
		Intron 5	Intron 5	C/t	0.89/0.11
		C1050T	Exon 8	C/t	0.56/0.44

to dietary modification. We know less, however, regarding the dramatic inter-individual variability observed during postprandial lipemia.

CONCLUSION

Multiple genes and environmental factors work in concert to alter these lipids. To fully understand the contribution of one particular genetic variant, many genetic variants in candidate genes involved in the lipid cascade must be evaluated. The table lists a number of loci that have been shown to contribute to variability in lipid phenotypes in the fasting and postprandial states and to CHD status.

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