UNIT NO. 1

EPIDEMIOLOGY OF HYPERLIPIDEMIA

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DISEASE BURDEN

Low density lipoprotein cholesterol (LDL-C), High density lipoprotein cholesterol (HDL-C) and triglyceride (TG) are major components of serum lipids that have been associated with atherosclerosis and CHD. Elevated LDL-C is well recognised as a causal risk factor for CHD. The serum cholesterol-CHD risk relationship is continuous, graded and curvilinear[1]. There is no threshold at which risk begins or a threshold below which there is no CHD risk. However, the risk conferred by any cholesterol level is highly dependent on concurrent risk factors and cannot be taken in isolation. In Singapore, 26.5% of the population had high LDL-C (L 4.1 mmol/l (160 mg/dl). If desirable LDL-C was taken as I 3.4 mmol/l, then 50.3% of the population in Singapore exceeded this level. Furthermore, 13.7% of our population had HDL-C that was deemed undesirable (I 1.0 mmol/l in males and I 1.3 mmol/l in females).

Coronary Heart Disease (CHD) is the major cause of mortality and morbidity in industrialised countries. CHD is epidemic across the industrialised countries and showing dramatic rise in many developing countries across Asia[2]. Given the high prevalence of high LDL-C and low HDL-C, it is not surprising that prevalence of CHD in Singapore is now comparable to many Western countries such as USA and Australia[3]. Ischaemic Heart Disease (24.2%) is the second highest cause of mortality in Singapore after cancer. However, cardiovascular disease (ischaemic heart disease and cerebrovascular disease) accounts for the highest cause of mortality (33%) in Singapore in 2002.

PATHOPHYSIOLOGY OF HYPERLIPIDEMIA

The original hypothesis of the pathogenesis of atherosclerosis was that of damage to the endothelium resulting in loss of endothelial cells. This was followed by platelet aggregation and release of platelet derived growth factor, which stimulated the proliferation of smooth muscle cells within the intima.

However, many of the early phases of atherosclerosis were not associated with endothelial loss or platelet aggregation. Instead, macrophages predominate in the early phases of atherosclerosis. Under normal circumstances, lipoproteins are too large to pass between endothelial cells to initiate atherosclerosis. Oxidation of lipoproteins such as LDL is one mechanism whereby the lipoproteins are altered so that it is recognised by receptors on macrophages. Hypertension, hypercholesterolemia and diabetes mellitus are conditions that can induce endothelial injury as well as favour oxidation of LDL. Endocytosis of the oxidised LDL occurs which result in transformation of macrophages to foam cells. When the foam cells appear, there is propagation of the atherosclerotic process through release of various growth promoters and inhibitors probably produced by the macrophage foam cells.

The main cholesterol carrying lipoproteins in the bodies are the LDL and HDL. In a normal individual, LDL contains approximately 70% and HDL 20% of the total plasma cholesterol. The main triglyceride-carrying lipoproteins are the chylomicrons and VLDLs. Most of the cholesterol present in the tissues are synthesized de novo rather than absorbed through diet. Although cholesterol is produced in many tissues, liver is the main site of synthesis in humans. The main rate limiting step in cholesterol synthesis is catalysed by HMG co-A reductase.

LDL receptors bind both Apo B-100 and Apo E containing lipoproteins and will therefore binds LDL-C and VLDL remnants. The role of the LDL receptors is to provide cholesterol to cells throughout the body and deliver excess cholesterol to the liver for recycling or excretion as bile acids. Hence, subjects with deficiency of LDL receptors (Familial Hypercholesterolemia) have high LDL-C. The LDL receptors can be down regulated when the level of intracellular free cholesterol rises. Statins reduce intracellular free cholesterol with a concomitant up regulation of LDL receptors and therefore reducing the serum LDL-C.

HDL receptors on the other hand are up regulated by rise in cholesterol levels. Reverse cholesterol transport takes place when free cholesterol is taken up by HDL from peripheral tissues, esterified and transferred to triglyceride rich lipoproteins and then transferred to the liver for disposal. This may account for the protective role of HDL-C.

EPIDEMIOLOGICAL EVIDENCE

The strong positive relationship between cholesterol levels and CHD did not stem from the Framingham Study alone but from several landmark epidemiological studies. The Seven countries study involved 12, 763 men from 16 different regions and seven countries demonstrated that the median cholesterol levels in each country were highly correlated with CHD mortality. Country such as Japan with low median cholesterol levels had low incidence of CHD mortality and the converse was true of countries with high median cholesterol levels such as Finland and USA. The Ni Hon San Study showed that as Japanese migrated from Japan to Hawaii or San Francisco, the rise in CHD events parallel the rise in cholesterol levels[4].

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FRAMINGHAM STUDY

The Framingham Study is a long term prospective, non interventional, epidemiological study in which a cohort of predominantly white subjects living in Framingham (outside Boston, USA) were followed up for more than 30 years. The study showed that as the cholesterol level rose, the CHD event rates rose concurrently[5]. The Framingham Study also showed that the risk of CHD rose steeply with the number of coexistent risk factors. The impact of high cholesterol was significantly greater when other CHD risk factor were present.

MULTIPLE RISK FACTOR INTERVENTION TRIAL

The most significant information from MRFIT was that serum cholesterol was related to CHD death in a continuous, graded manner. Subjects with cholesterol L 6.8 mmol/l had four fold CHD risk compared with subjects with cholesterol levels I 4.32 mmol/l[6]. The data also showed us that the absolute risk reduction with a reduction of serum cholesterol from 7.8 to 6.5 mmol/l was twice that obtained when serum cholesterol dropped from 6.5 to 5.2 mmol/l. This suggests that subjects with the highest risk derive the greatest benefit with cholesterol reduction compared with those with moderate or low risk.

CHD RISK FACTOR IN SINGAPORE

Major risk factors for CHD in Singapore are no different from those of western industrialised countries. These include hypercholesterolemia, low HDL-C, Diabetes Mellitus, Hypertension, smoking and obesity. What is particularly interesting in our context was the fact that ethnicity appears to play a significant role in CHD risk as those of Indian ethnicity appeared to have higher risk even after accounting for the traditional risk factors. Indians with diabetes have higher mortality compared with the other two ethnic groups[7]. On the other hand, the Malays had the highest LDL-C in our population. A detailed dietary survey showed that differences in diet alone could not explain the higher LDL-C seen in this particular ethnic group[8]. Malays were found to have twice the allele frequency of APOE4 genotype compared with the other two ethnic groups[9] and E4 is known to be associated with higher LDL-C. Although Indians as a group had lower HDL-C compared with Chinese or Malays, we have found that Indians with E2 had lower LDL-C and higher HDL-C. However, it is still unclear whether this would translate into benefits for Indians with E2 genotype. We believe that interactions between genes and environmental factors are likely to account for ethnic differences in lipid profile and CHD events amongst the ethnic groups in Singapore.

DIABETES MELLITUS

Diabetes Mellitus is a major contributor towards CHD events in Singapore. Given that 9.0% of our population has diabetes[10], with the majority being Type 2 DM, we can expect a significant rise in CHD events if the epidemic of diabetes mellitus is not contained. Diabetics are prone to accelerated atherosclerosis because of multiple risk factors. In Singapore, more than 90% of our diabetic population had LDL-C above 2.6 mmol/l (100 mg/dl), even those who were being treated for their diabetes. Given that diabetic patients should be treated as CHD risk equivalent, it is important that diabetic patients be aggressively treated for their lipid problems. Compounding this problem is the fact that most of them are also associated with low levels of HDL-C. The 1998 National Health Survey showed that 30.5% of the newly diagnosed diabetics had low levels of HDL-C (less than 1.0 mmol/l in males and less than 1.3 mmol/l in females) while 35.1% of known diabetics had low HDL-C. We have also previously reported that even if their lipid levels were "normal" a large majority carried dense LDL-C[11], which increases their atherogenic potential by 3 to 7 fold.

CONCLUSION

Hyperlipidemia and Diabetes Mellitus are two major risk factors which contribute to the high CHD events in Singapore. Dietary and lifestyle changes interacting with genetic profile have contributed to the ethnic differences observed such as that of Indians having 3 to 4 fold greater risk of CHD compared with the Chinese. Therefore, strategy to reduce CHD burdens must be cognizant of the peculiar distribution of CHD risk factors and the gene environment interaction in our population.

LEARNING POINTS

- Cardiovascular disease (Ischaemic heart disease and cerebrovascular disease) accounts for 33% of the mortality in Singapore in 2002
- Elevated low density lipoprotein cholesterol (LDL-C) is a well recognized causal risk factor for coronary heart disease
- There is no threshold at which risk begins or a threshold below which there is no coronary heart disease risk
- The strong positive relationship between cholesterol levels and coronary heart disease (CHD) stems not only from the Framingham Study alone but also from several landmark epidemiological studies
- Interactions between genes and environmental factors are likely to account for the ethnic differences in the lipid profile and CHD events amongst the ethnic groups in Singapore
- Diabetes mellitus is a major contributor towards CHD events in Singapore and it is important that diabetic patients are aggressively treated for their lipid problems.

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