UNIT NO. 2

EPIDEMIOLOGY OF ATHEROTHROMBOSIS

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ABSTRACT

Atherothrombotic cardiovascular disease is a global problem. With industrialization and urbanization, the disease burden is increasing at a faster rate in developing countries compared with developed countries. Various risk factors have been strongly linked with the development of atherothrombosis and control of these risk factors through lifestyle and pharmacological interventions can impact on outcome of at risk patients. Both the "population approach" and "high risk approach" should be used for primary prevention of atherothrombosis.

INTRODUCTION

The health status and disease profile of societies are linked to the level of economic development and social organization. With industrialization and urbanization, there is a shift in the major causes of death and disabilities from a predominance of nutritional deficiencies and infectious diseases to degenerative diseases such as cardiovascular diseases seen in the more advanced societies. This phenomenon is known as "the epidemiologic transition".[1]

DISEASE BURDEN

Global burden of cardiovascular disease

The 2003 World Health Report estimates that cardiovascular diseases account for 13% of the disease burden in adults above 15 years of age.[2] In addition, in older adults over the age of 60; ischemic heart disease and cerebrovascular disease are the two leading causes of death and disease burden. These two conditions are responsible for 36% of deaths in developed countries, and death rates are higher for men than women. There has been an increase in cardiovascular mortality in eastern European countries but this is offset by continuing declines in many developed countries. On the other hand, cardiovascular disease burden and mortality are rapidly increasing in developing countries. Between 1990 and 2020, the increase in ischemic heart disease mortality in the developing countries is expected to be much higher than in developed countries (120% vs. 29% in women and 137% vs. 48% in men respectively).[3] A similar pattern for increases in cerebrovascular disease mortality is predicted.

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Ethnic and geographic variations in disease rates

The ethnic and geographic variations in disease burden can be gleaned from the Seven Countries Study[4] and the 1997-1999 World Health Statistics[5]. For example, in the Seven Countries study, coronary artery disease (CAD) rates were low in Japan and the Mediterranean countries and high in Finland and the United States. Several factors may contribute to these observed interpopulation differences in cardiovascular profile:

1. Countries may be at different stages of the "epidemiologic transition" with differing contributions from competing causes of death.
2. Environmental factors related to atherothrombosis risk differ widely across populations and may be related to differing cultures as well as the level of urbanization and industrialization.
3. Genetic factors which may predispose certain populations to the risk factors of atherothrombosis.

Cardiovascular disease burden in Singapore

Cardiovascular disease is an important cause of mortality and morbidities in Singapore. Statistics from the Ministry of Health in 2003 revealed that ischemic and other heart diseases is the second commonest cause of death accounting for 24% of all deaths in 2002, a mortality rate that has remained steady from years 2000 to 2002.[6]

Cerebrovascular disease is the fourth commonest cause of death accounting for about 9% of all deaths. Both heart disease and cerebrovascular disease also accounted for about 9% of all hospitalizations in 2002. In addition, the latest Singapore National Health survey revealed ethnic differences in mortality from cardiovascular disease. South Indians were found to suffer higher mortality from cardiovascular disease compared with the Malays and Chinese.

RISK FACTORS FOR ATHEROTHROMBOSIS

There is a large body of evidence linking certain risk factors and the development of atherothrombosis.[7-12] These risk factors can be divided into two categories:

1. Causal risk factors – those for whom cause and effect association have been proven
   - elevated LDL cholesterol level
   - low HDL cholesterol level
   - tobacco consumption
   - hypertension
   - diabetes mellitus
   - physical inactivity*
   - obesity*
   - diet*.

2. Risk markers – those that show an association with atherothrombosis but for whom cause and effect relationship is not yet proven.
   - low socioeconomic status
   - elevated prothrombotic factors : fibrinogen, PAI-1
   - markers of infection or inflammation
   - elevated homocysteine
   - elevated lipoprotein (a)
   - psychological factors : depression, stress, acute life events etc.

* These factors are considered predisposing factors i.e. they are presumed to work, at least in part, through an impact on other risk factors that act directly e.g. obesity causes hypertension and dyslipidemia, both of which are causal risk factors for atherothrombosis.

Hypercholesterolemia, particularly elevated levels of LDL cholesterol, is the dyslipidemia most clearly associated with increased risk for atherothrombosis. A continuous and graded positive relation was demonstrated between total cholesterol level and CAD mortality in the Multiple Risk Factor Intervention Trial[7]. Similarly, an inverse relationship has been established between HDL cholesterol level and incidence of CAD e.g. in the Framingham Heart Study, men and women with HDL cholesterol of 35mg/dl or less had an eight fold increase in CAD incidence compared with those with HDL cholesterol of 65mg/dl or greater.[8] It is estimated that each mg/dl increase in HDL cholesterol decreases CAD risk by 2 percent in men and 3 percent in women.[9]

Epidemiological studies have linked cardiovascular diseases such as CAD, cerebrovascular disease and peripheral vascular disease with tobacco use. In the Framingham Heart Study, cardiovascular mortality increased 18 percent in men and 31 percent in women for each 10 cigarettes smoked per day.[10] The use of tobacco products in individuals with other risk factors was also found to have a synergistic effect on CAD mortality and morbidity e.g. smoking was found to increase the risk for cardiovascular diseases at every level of blood pressure. Smoking cessation in hypertensive patients who smoke one pack per day was estimated to reduce cardiovascular risk by 35 to 40 percent.

Numerous observational and epidemiological studies have established a direct relation between blood pressure elevation and incidence of CAD and stroke. In a meta-analysis of nine prospective studies that included 420, 000 patients without prior myocardial infarction or stroke and followed up for an average of 10 years, baseline blood pressure level was found to correlate with subsequent incidence rates of CAD death and non fatal myocardial infarction.[11]

Diabetes mellitus and the metabolic syndrome

Diabetes is a growing public health burden worldwide. By 2025, the number of people worldwide with diabetes is set to rise from the current estimate of 150 million to 300 million.[12] Most cases will be type 2 diabetes, which is strongly associated with a sedentary lifestyle and obesity. This trend of increasing prevalence of diabetes and obesity, even among children and adolescents, has already imposed a huge burden on healthcare systems and will continue to increase in the future.

There are two main forms of diabetes. Type 1 diabetes is caused primarily by autoimmune-mediated destruction of pancreatic beta-cell islets, resulting in absolute insulin deficiency. Type 2 diabetes is characterised by insulin resistance and/or abnormal insulin secretion, either of which may predominate.

One of the major consequences of type 2 diabetes is its association with extensive macrovascular and microvascular complications, resulting in significant premature morbidity and mortality. As a result of the insidious and silent progression from normal glucose tolerance to a pre-diabetes state (i.e., impaired glucose tolerance [IGT] and/or impaired fasting glucose [IFG]) to overt type 2 diabetes, susceptible individuals are often unaware of their disease status and may be exposed to long durations of hyperglycaemia without knowing. In addition, the concomitant burden of insulin resistance and related metabolic derangements (known as the metabolic syndrome, which often exists before the onset of overt diabetes), add to the toll of diabetic vascular complications. In fact, the vascular burden of type 2 diabetes is so high that it is now known that individuals with type 2 diabetes without coronary artery disease have the same risk of mortality as individuals with prior coronary artery disease without diabetes (i.e., type 2 diabetes may be regarded as coronary artery disease equivalent). Epidemiological evidence has also suggested that cardiovascular mortality is two to four-fold higher among individuals with diabetes.

A very useful resource is the UK Prospective Diabetes Study (UKPDS) Risk Engine, a programme that has been developed specifically for calculating the risk of coronary heart disease in individuals with type 2 diabetes. It is based on data collected from 5,102 patients, followed for up to 20 years. (http://www.dtu.ox.ac.uk/index.html?maindoc=/ukpds/).

Pre-menopausal women with type 2 diabetes are denied the cardioprotection associated with their pre-menopausal status (i.e., diabetes equalises the gender difference in risk for cardiovascular disease).[13] There is also accumulating evidence to suggest that susceptibility to vasculopathy differs among different ethnic groups. For instance, non-Hispanic white Americans with diabetes are more likely to develop macroangiopathy, such as myocardial infarction, stroke or peripheral vascular disease, compared with Asian and African Americans. However, Asian and African Americans with diabetes are more likely to develop microangiopathy (i.e., nephropathy) compared with Caucasian Americans.[14] Even among Asians, based on Singapore National Health Survey and National Disease Registry data, it has been reported that South Indians have higher mortality from cardiovascular disease compared with the Malays and Chinese.[15]

Type 2 diabetes is a multifactorial disease that shows heterogeneity in many respects. It is now recognised that type 2 diabetes is often a manifestation of a much broader underlying disorder. This may include the metabolic syndrome – a

cluster of cardiovascular risk factors that includes hyperinsulinaemia, dyslipidaemia, hypertension, visceral obesity, hypercoagulability and microalbuminuria, in addition to glucose intolerance. The exact aetiology of the metabolic syndrome is still unclear. Adiposity associated insulin resistance and endothelial dysfunction is believed to be the most likely culprit. The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Cholesterol in Adults (Adult Treatment Panel) in their third report indicate that three or more of the following risk factors constitute a diagnosis of the metabolic syndrome:[16]

- Waist Circumference >102 cm in men and >88 cm in women
- Triglyceride ³1.7 mmol/l
- HDL cholesterol <1.0 mmol/l in men and <1.3 mmol/l in women
- Blood pressure ³130/85 mmHg or known hypertensive on treatment
- Fasting glucose of ³6.1 mmol/l or known to have diabetes mellitus on treatment.

The World Health Organization criterion is more complex since it considers microalbuminuria, plasma insulin and body mass index (in place of waist circumference). Due to the unavailability of assays for insulin and microalbuminuria in Asia, the ATP III criteria are preferred.

These criteria may well change as new prospective data become available. However, the management of the metabolic syndrome is likely to be an important public health strategy in the fight against atherosclerotic cardiovascular diseases.

In contrast to type 1 diabetes, it is now well established that type 2 diabetes is a preventable disease (or can at least be retarded). Data from our 1992 National Health Survey cohort followed for eight years suggested conversion from IGT to type 2 diabetes at a rate of approximately 4% per year.[17] Four landmark clinical studies have unequivocally shown that intensive lifestyle modification (meal planning and exercise), resulting in modest weight reduction (5% to 7%), is highly effective in retarding the progression from IGT to type 2 diabetes. In addition, pharmacological interventions (metformin, acarbose and rosiglitazone), although less effective that lifestyle modification, are also useful in the prevention of type 2 diabetes. In fact, STOP-NIDDM (Study TO Prevent Non-Insulin-Dependent Diabetes Mellitus) suggested that treating IGT patients with acarbose is associated with a significant reduction in the risk of cardiovascular diseases and hypertension.[18] Therefore, the best prevention of diabetes-associated cardiovascular complications probably starts with the prevention of type 2 diabetes itself.

PREVENTING ATHEROTHROMBOSIS

Atherothrombotic cardiovascular disease is a global problem that affects every ethnic group. With increasing urbanization, the developing countries have seen a marked increase in disease burden. This is because the risk factor levels for atherothrombosis increase with urbanization. On the other hand, the developed countries have seen marked decline in atherothrombotic cardiovascular disease rates due to conscious efforts at both the societal level (for example legislation against tobacco advertisement), as well as the individual level (through risk factor modification and the use of effective evidence based medications).

Strategies for primary prevention of atherothrombosis can be divided into 2 groups[19]:

1. "Population approach": This strategy seeks to modify societal behaviours (such as healthy eating, discouraging tobacco use etc) and thereby influence the distribution of risk factors in the population at large. Even modest changes in risk factors can result in substantial reduction in risk of atherothrombosis in the population because of the large number of people involved. It aims to reduce the burden of disease in the whole community. However, it only confers small benefits to each individual.
2. "High risk approach": This strategy targets those at high risk for atherothrombosis because of their risk factor profile. It therefore provides large benefits to those at the highest risk but the benefits to the community at large may be limited because the numbers are few.

The "high risk approach" has yielded clear proof of efficacy for both lifestyle[20] and pharmacological interventions.[21-23] However, it must be noted that the majority of cardiovascular disease arise from the segment of population who exhibits only average levels of risk factors (i.e., they are only at modest risk). Therefore, the "high risk approach" should be complemented by the "population approach" to lower the "total risk of the population at large".

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LEARNING POINTS

1. **Atherothrombosis is a global problem that affects every ethnic group.**
2. **The disease burden is increasing at faster rate in developing countries compared with developed countries.**
3. **There is a large body of evidence linking various risk factors and the development of atherothrombosis.**
4. **Important risk factors include hypercholesterolemia, diabetes mellitus, tobacco consumption and hypertension.**
5. **Both the "population approach" and "high risk approach" should be used for primary prevention of atherothrombosis.**