Emerging Evidences from the Contribution of the Traditional and New Risk Factors to the Atherosclerosis Pathogenesis

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Atherosclerotic coronary artery disease accounts for the majority of cause of death in the world. A number of determinants most of them associated with lifestyle starting from early childhood onwards are responsible for Cardiovascular Diseases (CVD). Some risk factors facilitate the development of atherosclerosis, while others participate in the plaques formation, resulting in the manifestation of the disease. The major risk factors for CVD such as those results from metabolic disturbances as in high blood pressure, diabetes, obesity and elevated blood cholesterol levels and lifestyle related factors such as cigarette smoking and lack of physical activity continued to represent the center of investigation for all possible mechanism. However, a host of new mechanisms involving new unconventional risk factors such as air pollution, immunity and infection are also under extensive investigation. As a result; potential markers for CVD risk stratification have emerged. This study is an attempt to provide an over view of the current understanding of CVD pathophysiology stressing the role of new emerging players in the development of the disease.

Key words: Cardiovascular disease, physical inactivity, obesity, chronic kidney disease, platelets, air pollution

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INTRODUCTION

Cardiovascular Diseases (CVD) remains the major cause of morbidity and mortality in developed countries and now a growing concern beside the infection diseases in the developing countries as the leading cause of death in these countries. According to the World Health Organization; CVDs are the number one cause of death globally, more people die annually from a CVD than from any other cause. An estimated 17.5 million people died from CVD in 2005, representing 30% of all global deaths. Of these deaths, an estimated 7.6 million were due to coronary heart disease and 5.7 million were due to stroke. Over 80% of CVD deaths take place in low- and middle-income countries and occur almost equally in men and women; by 2015, almost 20 million people will die from CVD; mainly from heart disease and stroke (WHO, 2008). CVD is now increasing in developing countries.

In many industrialized countries, death rates peaked in the 1960s and early 1970s and have since declined dramatically. In Australia, New Zealand and United States for example, IHD deaths have fallen by over 50% since, the mid-1960s. However, according to the American Heart Association (Heart Disease and Stroke Statistics, 2009), the prevalence of CVD in USA in the year of 2006 was 36.3% affecting 80 million Americans.

THE RISK FACTORS LIST IS GROWING

Early epidemiological studies in the past five decades basic and epidemiological research have shown conclusively that a number of determinants most of them associated with lifestyle starting from early childhood onwards are responsible for CVD. Some risk factors participate in the development of atherosclerosis, while others are part of the formation of plaques, producing the clinical manifestation (Meade et al., 1986; Grundy et al., 2000; Tracy, 1998; Ross, 1999; Libby and Ridker, 1999). Major risk factors for CVD such as those which are part of the metabolic process represented by high blood pressure, diabetes, obesity and elevated blood cholesterol levels and life style related factors such as cigarette smoking and lack of physical activity; are responsible for about 80% of Coronary Heart Disease (CHD) and cerebrovascular disease; whereas others which are characterized, as non-modifiable factors such as genetics disposition, age and sex and ethnicity, remained the primary causes of CVD. However, in addition to these factors, new emerging evidences link CVD to dietary habits, type of fats and environmental factors including air pollution, stress and mental wellbeing. Efforts to prevent or treat some of these risk factors have improved overall contribution of these factors in CAD (Parthasarathy, 1994; Rosin, 2007; Le and Walker, 2007). However, on the hand some of the risk factors such as physical inactivity and obesity have continued to contributor to CVD epidemiology and represent a public health concern (Fig. 1).

MARKERS OF INFLAMMATION AND OXIDATIVE STRESS IN RECENT STUDIES

Several studies have attempted to demonstrate the presence of oxidized low-density lipoprotein (OxLDL) in

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Fig. 1: Risk factors of atherosclerosis. Group of interrelated risk factors influence the development of atherosclerosis including life style, diseases of metabolic disturbances and environment.
atherosclerotic lesions. The in vivo presence of Ox-LDL has been reviewed elsewhere in detail and will not be elaborated extensively (Cronwell and Otvos, 2004; Yla-Herttuala et al., 1990a; Gareirabi et al., 2008a; Haberland et al., 1988; Palmiini et al., 1989). It should be noted that to date the evidence for the presence of Ox-LDL is confined to atherosclerotic tissue. Immunocytochemical techniques have demonstrated the presence in arterial lesions, but not in normal arteries. Also, there are convincing evidences from the role of oxidative modification in lesion formation that comes from studies demonstrating that antioxidants such as probucol (Jachoder et al., 2008; Boyd et al., 1989; Parthasarathy, 1992; Yla-Herttuala et al., 1990b, 1991) or butylated hydroxytoluene can inhibit lesion formation in WHHL rabbits and cholesterol-fed rabbits, respectively. In the case of the probucol experiments, it was specifically demonstrated that probucol inhibited the uptake and degradation of LDL in macrophage-rich lesions, while not inhibiting such uptake in normal arterial tissue (Shao et al., 2006; Parthasarathy et al., 2008; Chisolm and Steinberg, 2000; Berliner, 2002; Matsuura et al., 2006). This review will attempt to provide insight on the new developments in the field and therefore will not discuss in details the background of the oxidation and inflammation theories in atherosclerosis.

Researchers continued to explore new markers involved in the pathophysiology of Cardiovascular Disease (CVD), provide evidences for, diagnosis, risk stratification, prevention and treatment strategy. Strategies for the identification of inflammatory markers had been reviewed by the American Heart Association Study group constituted to evaluate potential new markers and they have concluded many of these markers (including inflammatory markers) are not yet considered applicable for routine risk assessment because of (WF6O, 2008) lack of measurement standardization, lack of consistency in epidemiological findings from prospective studies with endpoints and (Meade et al., 1986) lack of evidence that the novel marker adds to risk prediction over and above that already achievable through the use of established risk factors (Pearson et al., 2003). Since, the AHA release numbers of inflammatory markers has been studied and have provided valuable clues. Among these markers, C-Reactive Protein (CRP) has been reviewed extensively (Henrikson et al., 1983; Blake and Ridker, 2003; Ridker et al., 2007) and continued to provide evidences for risk stratification. In the recent JUPITER trial; a large multinational, long-term, double-blind, placebo-controlled, randomized clinical trial designed to assess whether statin therapy (rosuvastatin 20 mg 'day') should be given to apparently healthy individuals with low LDL-cholesterol levels but elevated C-Reactive-Protein (CRP) levels. Individuals with low Low-Density Lipoprotein (LDL) cholesterol but elevated CRP levels had shown significantly reduced the primary end. Reductions in CRP and LDL are equally effective in predicting the efficacy of rosuvastatin. Low-risk primary prevention in populations with raised LDL cholesterol or hsCRP, would involve a lifestyle change such as dietary restriction, exercise and smoking cessation. CRP, a marker of inflammation, has become a widely accepted in clinical practice and the test is relatively inexpensive and has a rapid turnover. The Physician's Health Study was the first large-scale prospective study to show that the relative risk of first myocardial infarction or stroke directly related to hsCRP levels (Ridker et al., 2008). Other inflammatory markers that are receiving some attention currently include lipoprotein associated phospholipase A2 (Lp-PLA2), which is produced by macrophages and circulates bound predominantly to Low Density Lipoproteins (LDL), (Rosenson, 2010; Thompson et al., 2010, White, 2010). CD40 ligand, produced by endothelial cells, smooth muscle cells and activated platelets is another biomarker that is currently investigated. A soluble form of the CD40 ligand is measurable in plasma (Zakynthinos and Pappa, 2009). A significant percentage of non-lipid factors including genetic mutations, inflammation, coagulation disorders, infection and markers of autoimmune disease are also considered for their role in the pathogenesis of CAD (Beaudo et al., 2004; Vovo et al., 2003; Steinbrecher et al., 1984; Gareinpi et al., 2008b; National Cholesterol Education Program, 2004; Steinberg and Lewis, 1997; Steinberg et al., 1989; Hessler et al., 1983) (Table 1).

Matrix metalloproteinases (MMPs) extracellular enzymes are regulated mainly by Tissue Inhibitors of Metalloproteinases (TIMPs). MMPs expression is connected with the conventional cardiovascular risk factors as well as with inflammation. They play a central role in atherosclerosis, plaque formation, platelet aggregation, acute coronary syndrome, restenosis, aortic aneurysms and peripheral vascular disease. Numbers of studies have shown that antihypertensive medications and lipid lowering statins may influence MMPs activity (Kai et al., 1998; Blankenberg et al., 2003; Visknesvsky et al., 2004; Morel et al., 1984; Haberland et al., 1984, 1982; Young et al., 2003).

As an atherosclerosis development precedes the cardiovascular disease, identification of such markers are of great importance (Fig. 2).
Table 1: Selected cardiovascular biomarkers

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Clinical significance</th>
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<tr>
<td>Angiotensin Converting Enzyme (ACE) polymorphism (insertion/deletion)</td>
<td>Heterozygous or homozygous, increases risk of CAD and restenosis</td>
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<tr>
<td>Activated protein C resistance (APC-R)</td>
<td>Its presence increased risk for venous thromboembolic disease, Cardiovascular disease (particularly in women &gt;50) and cerebrovascular disease, associated with acute phase reactions</td>
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<tr>
<td>B-type natriuretic peptide (BNP) cystatin C</td>
<td>Indicated in heart failure, increases risk of future cardiac events Marker of chronic kidney disease and CVD</td>
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<td>Beta2-Glycoprotein I antibodies</td>
<td>Increases risk for cardiovascular and cerebrovascular diseases and thromboembolic disease associated with recurrent fetal loss, thrombocytopenia and systemic lupus erythematosus (SLE)</td>
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<tr>
<td>Chlamydia pneumoniae antibodies</td>
<td>Presences of infection; increases CVD risk</td>
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<tr>
<td>Cytomegalovirus (CMV) antibodies</td>
<td>Presences of infection; increases CVD risk</td>
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<tr>
<td>Helicobacter pylori antibody</td>
<td>Indicators of oxidative stress and they increases in chronic diseases including CVD</td>
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<td>Oxidation markers: Thiobarbituric acid reactive substances (TBARS), Oxidized Low Density Lipoproteins (OxLDL), Myeloperoxidase (MPO) and 8-iso-Prostaglandin F2alpha (8-isoprostane)</td>
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<tr>
<td>Inflammation molecules: hsCRP, Cytokines IL6, IL2, IL8 and TNF and Chemotactic cytokines (MCP1)</td>
<td>Mediators and indicators of inflammation and atherosclerosis</td>
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<tr>
<td>Adhesion Molecules: ICAM-1, SCAVM1, selectins</td>
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Fig. 2: From atherosclerosis to plaque rupture. Within the vascular system pro-oxidant molecules modify LDL, side by side with the inflammation processes influence the development of atherosclerosis leading to buildup of the fatty streak in the sub-endothelium and the formation of the atherosclerotic plaque. A rupture of the plaque will trigger a coagulation cascade resulting in CVD.

DIET, PHYSICAL INACTIVITY AND OBESITY

Considerable amount of data suggest that physical activity would moderately attenuate but did not eliminate the adverse effect of obesity on cardiovascular disease. It is also reported that a reduced BMI would not benefit to reduce the risk associated with the physical inactivity (Blair, 2003; Blair and Church, 2004; Church et al., 2005; Hu et al., 2001; LaMonte and Blair, 2006; Li et al., 2006; Tanasiecu et al., 2003; Moreno et al., 2006). Recent studies on exercise and body weight suggest that the current exercise guidelines, which proposes a daily 30 min
of moderate activity is quite insufficient if not accompanied by a controlled dietary intake. Dietary restriction combined with endurance exercise training represents an effective way to promote weight loss and reduce fat mass in obese people (Wei et al., 2005; Van Gaal et al., 2006; Hu et al., 2004). Exercise regimen without dietary restriction was shown to be less effective. However, addition of exercise to a dietary restriction does not induce a greater fat-mass loss than dietary restriction alone (Rana et al., 2007; Jurca et al., 2005; Blair and LaMonte, 2005; Saris et al., 2003; Jeon et al., 2007; Qi et al., 2006). The latter is likely attributed to a compensatory reduction in daily physical activity following the implementation of exercise training. Nonetheless, inclusion of an exercise training bout is important to obese patients in order to achieve the maximum benefits of combined treatment. Regular exercise training as part of a multifactorial intervention improves symptoms in patients with CAD, augments myocardial perfusion and reduces mortality of these patients; the regression of atherosclerosis, the formation of collaterals and the partial correction of endothelial dysfunction as a consequence of molecular adaptations are well linked to physical activity (He et al., 2004; Leermakers et al., 2000; Martinez-Gonzalez et al., 1999; Strasser and Pichler, 2004). However, the positive effects of exercise training in primary and secondary prevention of cardiovascular diseases goes way beyond to the adipose tissues and improve the overall biochemical performance of this tissues (Mijailovi et al., 2004; Dao et al., 2004; Borg et al., 2004). Regular physical activity, either alone or as part of a multifactorial intervention consisting of diet and exercise training, is known to promote effective weight loss especially in patients with metabolic syndrome, weight reduction beneficially effects blood glucose control.

Recent statement by the American College of Sports Medicine (ACSM) has promoted the physical activity in older adults and emphasizes moderate-intensity aerobic activity, muscle-strengthening activity, reducing sedentary behavior and risk management (Blair, 2003). Exercise recommendations to treat or prevent obesity have focused mainly on aerobic activities. Diet rich in fat and contains high amounts of peroxidized fat is of great concern. Rise in postprandial plasma triglycerides is well studied and linked to diabetes and cardiovascular as consequences of such diet. Dietary trans-fatty acids are another element of lipids that is implicated in increased risk of cardiovascular disease (Parthasarathy et al., 2008). Large controlled trials have shown that intake of fish oil (marine n-3 fatty acids, eicosapentaenoic acid and docosahexaenoic acid), whether from dietary sources or fish oil supplements, may reduce cardiovascular disease mortality (De Leiris et al., 2009; Simopoulos, 1991). Although a large body of evidence supports that dietary intake of polyphenols-particularly of flavonoids such as flavanols may reduce the risk for cardiovascular through their antioxidants properties, CVD antioxidants clinical trials outcome did not prove to be beneficial (Pitasos et al., 2005; Williamson et al., 2005).

Adherence to dietary guidelines is beneficial for CVD risk reduction. A study conducted at the USDA Human Nutrition Research Center which examined data on eating patterns of 224 postmenopausal women who had coronary artery disease and also used imaging to examine the development of atherosclerosis in these women, have shown that women who have shown greater adherence to the dietary guidelines had less progression on their atherosclerotic lesions over a three-year period (Imamura et al., 2009). These finding stress the need for dietary intervention as part of the prevention and treatment regimen for CVD.

EFFECT OF AIR POLLUTION ON THE DEVELOPMENT ATHEROSCLEROSIS

Airborne particulate matter, from higher exposure to outdoor air pollution engine exhaust and other sources, or indoor cooking oil and smoking, is linked to increased cardiopulmonary deaths, but there is limited evidence of the association of outdoor air pollution and cardiovascular disease (Sun et al., 1994; Cakir et al., 2007; Tamagawa et al., 2008). Experiments on the development of atherosclerosis and CVD are mainly performed in animals using confined environments for extended period of time which may not necessarily resembles the process in human. The field of air pollution and CVD is newly emerging despite the fact that air quality studies have started several decades ago. In the mid of the last decade, concerns about the health effects of air pollution had prompted several epidemiological studies (Kunzli et al., 2008). These studies have brought awareness about air quality standards and guidelines and a dramatic increase in health-related air pollution research which is centered on respiratory disease. In a recent study investigators exposed rats to oil smoke for 120 min with or without 20 min pretreatment with lovastatin have shown that particulate matter can mediate CVD through development of thrombosis involving substance P and its receptor, the NK-1 receptor and reactive oxygen radicals (Rudaz et al., 2009). In another study conducted in Netherland on 40 volunteers over a year time, investigators have reported that air pollution increased platelet aggregation as well as coagulation activity but not inflammation markers (Forbes et al., 2009). These prothrombotic effects may
partly explain the relationship between air pollution and the risk of ischemic cardiovascular disease (Mills et al., 2009). The pollutant Diesel Exhaust (DE) is reported to increase endothelin (ET) levels, suggesting this may contribute to DE-induced cardiovascular disease (Lund et al., 2007). A study from Milan, Italy recently published investigating the link between living near major traffic roads and increases risk of Deep Vein Thrombosis (DVT) in cities with population >15,000 inhabitants in Lombardia Region, Italy from 1995 through 2005 included 663 patients with DVT of the lower limbs and 859 age-matched controls have concluded that living near major traffic roads is associated with increased risk of DVT (Baccarelli et al., 2009).

These reports open the door for more studies on basic science and clinical research to investigate possible mechanisms for the involvement of air pollution in risk for CVD.

CONCLUSION

We reviewed atherosclerosis and resultant CVD pathophysiology. New mechanisms on the role of oxidative stress and inflammation continued to be investigated and potential markers are emerging. Data from dietary intervention, obesity and physical inactivity have provided valuable clues on the progression of the disease. Studies on the role of air pollution although mainly conducted in animal models, have shown promising breakthrough in this emerging area.

REFERENCES


