Journal of Medical Sciences

ISSN 1682-4474

science alert

ANSInet
an open access publisher
http://ansinet.com

Review Article

J. Med. Sci., 10 (6): 153-161
15th August, 2010

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

Mahdi Garelnabi

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 life style 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 pollutions, 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

JMS (ISSN 1682-4474) is an International, peer-reviewed scientific journal that publishes original article in experimental & clinical medicine and related disciplines such as molecular biology, biochemistry, genetics, biophysics, bio-and medical technology. JMS is issued eight times per year on paper and in electronic format.

For further information about this article or if you need reprints, please contact:

Mahdi Garelnabi
Department of Clinical Laboratory and Nutritional Sciences, School of Health and Environment, University of Massachusetts Lowell, 61 Wilder, Lowell, MA 01854, Suite 319, Lowell, USA

Tel: 978-934-4528
Fax: 978-934-4021

ANSInet
Asian Network for Scientific Information

Department of Clinical Laboratory and Nutritional Sciences, University of Massachusetts Lowell, MA, USA

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 Walter, 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

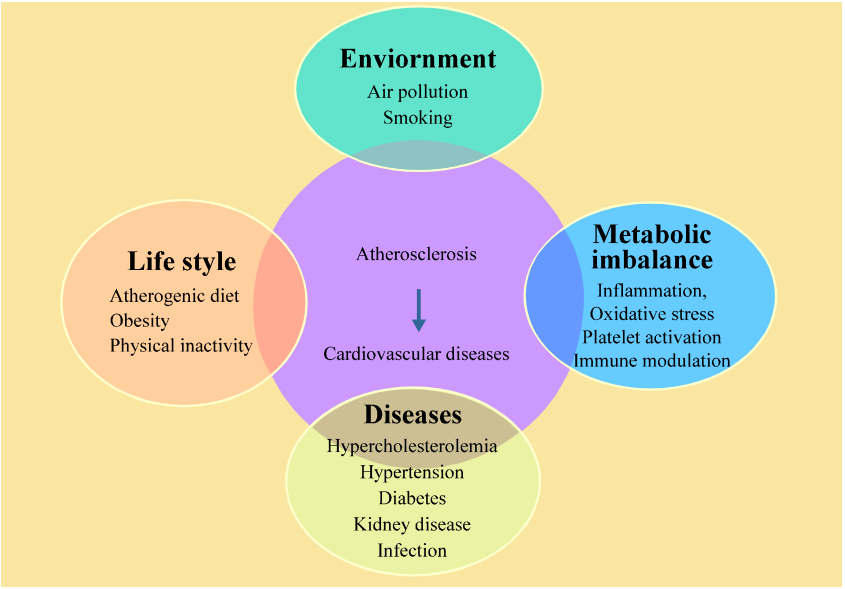

Fig. 1: Risk factors of atherosclerosis. Group of interrelated risk factors influence the development of atherosclerosis including life style, diseases of metabolic disturbances and environment

atherosclerotic lesions. The *in vivo* presence of Ox-LDL has been reviewed elsewhere in detail and will not be elaborated extensively (Cromwell and Otvos, 2004; Yla-Herttuala *et al*., 1990a; Garelnabi *et al*., 2008a; Haberland *et al*., 1988; Palinski *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 (Jaichander *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 (WHO, 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 (Henriksen *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^{-1}) 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 (Beaudeux *et al*., 2004; Varo *et al*., 2003; Steinbrecher *et al*., 1984; Garelnabi *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; Vishnevetsky *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

Biomarker	Clinical significance
Angiotensin Converting Enzyme (ACE)) polymorphism (insertion/deletion)	Heterozygous or homozygous, increases risk of CAD and restenosis
Activated protein C resistance (APC-R)	Its presence increased risk for venous thromboembolic disease, Cardiovascular disease (particularly in women >50) and cerebrovascular disease; associated with acute phase reactions
B-type natriuretic peptide (BNP) cystatinC	Indicated in heart failure, increases risk of future cardiac events Marker of chronic Kidney disease and CVD
Beta2-Glycoprotein I antibodies	Increases risk for cardiovascular and cerebrovascular diseases and thromboembolic disease associated with recurrent fetal loss, thrombocytopenia and systemic lupus erythematosus (SLE)
Chlamydia pneumoniae antibodies	Presences of infection; increases CVD risk
Cytomegalovirus (CMV) antibodies	Presences of infection; increases CVD risk
Helicobacter pylori antibody	Presences of infection; increases CVD risk
Oxidation markers: Thiobarbituric acid reactive substances (TBARS), Oxidized Low Density Lipoproteins (OxLDL), Myloperoxidase (MPO) and 8-iso-Prostaglandin F2alpha (8-isoprostane)	Indicators of oxidative stress and they increases in chronic diseases including CVD
Inflammation molecules:	
hsCRP; Cytokines IL6, IL2, IL8 and TNF-α, Chemotactic cytokines (MCP1) Adhesion Molecules: ICAM-1, SVCAM1, selectins	Mediators and indicators of inflammation and atherosclerosis

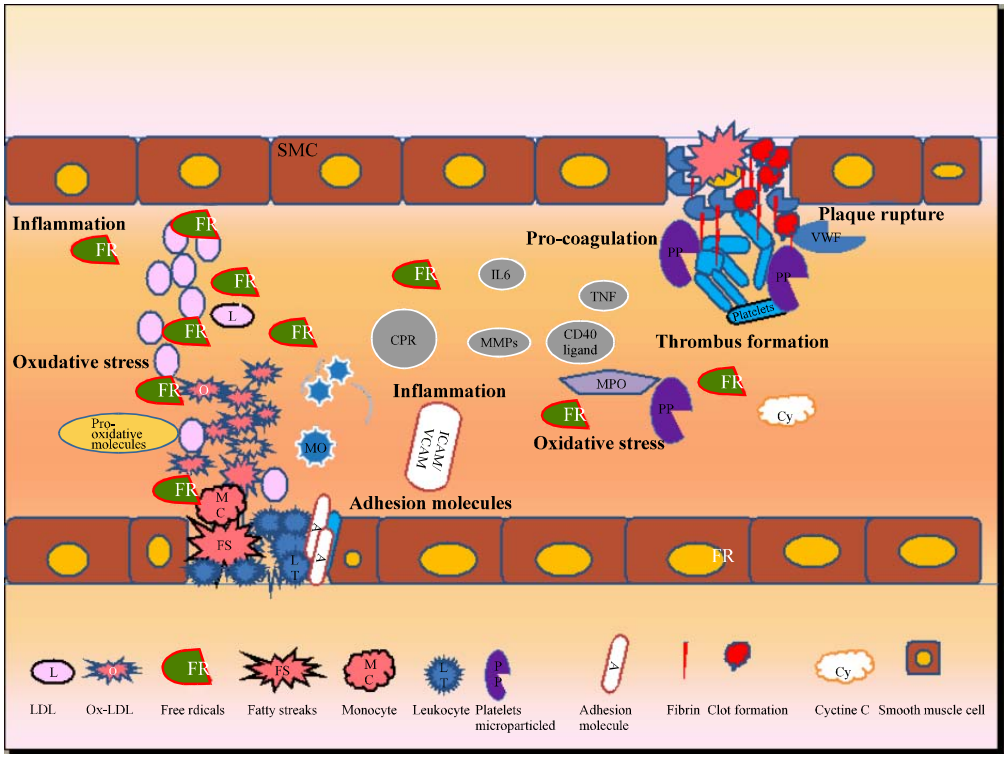

Fig. 2: From atherosclerosis to plaque rupture. Within the vascular system pro-oxidant molecules modify LDL, side by side with the inflammation processes influence the development of atherosclerosis leading to buildup of the fatty streak in the sub-endothelium and the formation of the atherosclerotic 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 attenuated 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; Tanasescu *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 boat 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 (ASCM) 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 (Pitsavos *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 (Rudez *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

Baccarelli, A., I. Martinelli, V. Pegoraro, S. Melly and P. Grillo *et al*., 2009. Living near major traffic roads and risk of deep vein thrombosis. Circulation, 119: 3118-3124.

Beaudeux, J.L., P. Giral, E. Bruckert, M.J. Foglietti and M.J. Chapman, 2004. Matrix metalloproteinases, inflammation and atherosclerosis: Therapeutic perspectives. Clin. Chem. Lab. Med., 42: 121-131.

Berliner, J., 2002. Introduction lipid oxidation products and atherosclerosis. Vascul. Pharmacol., 38: 187-191.

Blair, S.N., 2003. Physical activity, epidemiology, public health and the American college of sports medicine. Med. Sci. Sports Exerc., 35: 1463-1463.

Blair, S.N. and T.S. Church, 2004. The fitness, obesity and health equation: Is physical activity the common denominator?. JAMA, 292: 1232-1234.

Blair, S.N. and M.J. LaMonte, 2005. How much and what type of physical activity is enough? What physicians should tell their patients. Arch Intern. Med., 165: 2324-2325.

Blake, G.J. and P.M. Ridker, 2003. C-reactive protein and other inflammatory risk markers in acute coronary syndromes. J. Am. Coll. Cardiol., 41: 37S-42S.

Blankenberg, S., H.J. Rupprecht, O. Poirier, C. Bickel and M. Smieja *et al*., 2003. Plasma concentrations and genetic variation of matrix metalloproteinase 9 and prognosis of patients with cardiovascular disease. Circulation, 107: 1579-1585.

Borg, P., M. Fogelholm and K. Kukkonen-Harjula, 2004. Food selection and eating behaviour during weight maintenance intervention and 2-y follow-up in obese men. Int. J. Obes. Relat. Metab. Disord., 28: 1548-1554.

Boyd, H.C., A.M. Gown, G. Wolfbauer and A. Chait, 1989. A direct evidence for a protein recognized by a monoclonal antibody against oxidatively modified LDL in atherosclerosis lesions from a *Watanabe heritable* Hyperlipidemic rabbit. Am. J. Pathol., 135: 815-825.

Cakir, Y., Z. Yang, C.A. Knight, M. Pompilius and D. Westbrook *et al*., 2007. Effect of alcohol and tobacco smoke on mtDNA damage and atherogenesis. Free Radic. Biol. Med., 43: 1279-1288.

Chisolm, G.M. and D. Steinberg, 2000. The oxidative modification hypothesis of atherosclerosis: An overview. Free Radic. Biol. Med., 28: 1815-1826.

Church, T.S., M.J. La Monte, C.E. Barlow and S.N. Blair, 2005. Cardiorespiratory fitness and body mass index as predictors of cardiovascular disease mortality among men with diabetes. Arch Intern. Med., 165: 2114-2120.

Cromwell, W.C. and J.D. Otvos, 2004. Low-density lipoprotein particle number and risk for cardiovascular disease. Curr. Atheroscler. Rep., 6: 381-387.

Dao, H.H., M.L. Frelut, F. Oberlin, G. Peres, P. Bourgeois and J. Navarro, 2004. Effects of a multidisciplinary weight loss intervention on body composition in obese adolescents. Int. J. Obes. Relat. Metab Disord., 28: 290-299.

De Leiris, J., M.D. Lorgeril and F. Boucher, 2009. Fish oil and heart health. J. Cardiovasc. Pharmacol., 54: 378-384.

Forbes, L.J., M.D. Patel, A.R. Rudnicka, D.G. Cook and T. Bush *et al*., 2009. Chronic exposure to outdoor air pollution and diagnosed cardiovascular disease: Meta-analysis of three large cross-sectional surveys. Environ. Health, 8: 30-30.

Garelnabi, M.O., W.V. Brown and N.A. Le, 2008a. Evaluation of a novel colorimetric assay for free oxygen radicals as marker of oxidative stress. Clin. Biochem., 41: 1250-1254.

Garelnabi, M., K. Selvarajan, D. Litvinov, N. Santanam and S. Parthasarathy, 2008b. Dietary oxidized linoleic acid lowers triglycerides via APOA5/APOCIll dependent mechanisms. Atherosclerosis, 199: 304-309.

Grundy, S.M., T. Bazzarre, J. Cleeman, R.B. Sr. D'Agostino, M. Hill and N. Houston-Miller, 2000. Prevention conference V: Beyond secondary prevention: Identifying the high-risk patient for primary prevention: Medical office assessment: Writing Group III. Circulation, 101: E3-E11.

Haberland, M.E., A.M. Fogelman and P.A. Edwards, 1982. Specificity of receptor-mediated recognition of malondialdehyde-modified low density lipoproteins. PNAS, 79: 1712-1716.

Haberland, M.E., C.L. Olch and A.M. Fogelman, 1984. Role of lysines in mediating interaction of modified low density lipoproteins with the scavenger receptor of human monocyte macrophages. J. Biol. Chem., 259: 11305-11311.

Haberland, M.E., D. Fong and L. Cheng, 1988. Malondialdehyde-altered protein occurs in atheroma of Watanabe heritable hyperlipidemic rabbits. Science., 241: 215-218.

He, K., F.B. Hu, G.A. Colditz, J.E. Manson, W.C. Willett and S. Liu, 2004. Changes in intake of fruits and vegetables in relation to risk of obesity and weight gain among middle-aged women. Int. J. Obes., 28: 1569-1574.

Heart Disease and Stroke Statistics, 2009. A report from the american heart association statistics committee and stroke statistics subcommittee. Circulation, 119: e1-e161.

Henriksen, T., E.M. Mahoney and D. Steinberg, 1983. Enhanced macrophage degradation of biologically modified low density lipoprotein. Arteriosclerosis, 3: 149-159.

Hessler, J.R., D.W. Morel, L.J. Lewis and G.M. Chisolm, 1983. Lipoprotein oxidation and lipoprotein-induced cytotoxicity. Arteriosclerosis, 3: 215-222.

Hu, F.B., M.J. Stampfer, C.Solomon, S. Liu and G.A. Colditz *et al*., 2001. Physical activity and risk for cardiovascular events in diabetic women. Ann. Intern. Med., 134: 96-105.

Hu, F.B., W.C. Willett, T. Li, M.J. Stampfer, G.A. Colditz and J.E. Manson, 2004. Adiposity as compared with physical activity in predicting mortality among women. N. Engl. J. Med., 351: 2694-2703.

Imamura, F., P.F. Jacques, D.M. Herrington, G.E. Dallal and A.H. Lichtenstein, 2009. Adherence to 2005 Dietary guidelines for Americans is associated with a reduced progression of coronary artery atherosclerosis in women with established coronary artery disease. Am. J. Clin. Nutr., 90: 193-201.

Jaichander, P., K. Selvarajan, M. Garelnabi and S. Parthasarathy, 2008. Induction of paraoxonase 1 and apolipoprotein A-I gene expression by aspirin. J. Lipid Res., 10: 2142-2148.

Jeon, C.Y., R.P. Lokken, F.B. Hu and R.M. van Dam, 2007. Physical activity of moderate intensity and risk of type 2 diabetes: A systematic review. Diabetes Care, 30: 744-752.

Jurca, R., A.S. Jackson, M.J. LaMonte, J.R.Jr. Morrow and S.N. Blair *et al*., 2005. Assessing cardiorespiratory fitness without performing exercise testing. Am. J. Prev. Med., 29: 185-193.

Kai, H., H. Ikeda, H. Yasukawa, M. Kai and Y. Seki *et al*., 1998. Peripheral blood levels of matrix metalloproteases-2 and -9 are elevated in patients with acute coronary syndromes. J. Am. Coll. Cardiol., 32: 368-372.

Kunzli, N., L. Perez, F. Lurmann, A. Hricko, B. Penfold and R. McConnell, 2008. An attributable risk model for exposures assumed to cause both chronic disease and its exacerbations. Epidemiology, 19: 179-185.

LaMonte, M.J. and S.N. Blair, 2006. Physical activity, cardiorespiratory fitness and adiposity: Contributions to disease risk. Curr. Opin. Clin. Nutr. Metab. Care, 9: 540-546.

Le, N.A. and M.F. Walter, 2007. The role of hypertriglyceridemia in atherosclerosis. Curr. Atheroscler. Rep., 9: 110-115.

Leermakers, E.A., A.L. Dunn and S.N. Blair, 2000. Exercise management of obesity. Med. Clin. North Am., 84: 419-440.

Li, T.Y., J.S. Rana, J.E. Manson, W.C. Willett and M.J. Stampfer *et al*., 2006. Obesity as compared with physical activity in predicting risk of coronary heart disease in women. Circulation, 113: 499-506.

Libby, P. and P.M. Ridker, 1999. Novel inflammatory markers of coronary risk. Circulation, 100: 1148-1150.

Lund, A.K., T.L. Knuckles, C.O. Akata, R. Shohet and J.D. McDonald *et al*., 2007. Gasoline exhaust emissions induce vascular remodeling pathways involved in atherosclerosis. Toxicol. Sci., 95: 485-494.

Martinez-Gonzalez, M.A., J.A. Martínez, F.B. Hu, M.J. Gibney and J. Kearney, 1999. Physical inactivity, sedentary lifestyle and obesity in the European Union. Int. J. Obes., 23: 1192-1201.

Matsuura, E., K. Kobayashi, M. Tabuchi and L.R. Lopez, 2006. Oxidative modification of lowdensity lipoprotein and immune regulation of atherosclerosis. Prog. Lipid Res., 45: 466-486.

Meade, T.W., S. Mellows, M. Brozovic, G.J. Miller and R.R. Chakrabarti *et al*., 1986. Haemostatic function and ischemic heart disease: Principal results of the northwick park heart study. Lancet, 2: 533-537.

Mijailovi, V., D. Mici and M. Mijailovi, 2004. Effects of a one-year weight reduction program and physical activity on obesity and comorbid conditions. Med. Pregl., 57: 55-59.

Mills, N.L., K. Donaldson, P.W. Hadoke, N.A. Boon and W. MacNee *et al*., 2009. Adverse cardiovascular effects of air pollution. Nat. Clin. Pract. Cardiovasc. Med., 6: 36-44.

Morel, D.W., P.E.D. Corleto and G.M. Chisolm, 1984. Endothelial and smooth muscle cells alter low density lipoprotein *in vitro* by free radical oxidation. Arteriosclerosis, 4: 357-364.

Moreno, L.A., M.G. Blay, G. Rodriguez, V.A. Blay and M.I. Mesana *et al*., 2006. Screening performances of the international obesity task force body mass index cut-off values in adolescents. J. Am. Coll. Nutr., 25: 403-408.

National Cholesterol Education Program, 2004. Implications of Recent Clinical Trials for the ATP III Guidelines. National Heart, Lung and Blood Institute, Bethesda, MD.

Palinski, W., M.E. Rosenfeld, S.Y. Herttuala, G.C. Gurtner and S.S. Socher *et al*., 1989. Low density lipoprotein undergoes oxidative modification *in vivo*. PNAS, 86: 1372-1376.

Parthasarathy, S., 1992. Evidence for an additional intracellular site of action of probucol in the prevention of oxidative modification of low density lipoprotein: Use of a new water-soluble probucol derivative. J. Clin. Invest., 89: 1618-1621.

Parthasarathy, S., 1994. Modified Lipoproteins in the Pathogenesis of Atherosclerosis. R.G. Landes Co., Austin, TX., pp: 131.

Parthasarathy, S., D. Litvinov, K. Selvarajan and M. Garelnabi, 2008. Lipid peroxidation and decomposition-conflicting roles in plaque vulnerability and stability. Biochimica et Biophysica Acta, 1781: 221-231.

Pearson, T.A., G.A. Mensah, R.W. Alexander, J.L. Anderson and R.O. Cannon *et al*., 2003. Markers of inflammation and cardiovascular disease: Application to clinical and public health practice: A statement for healthcare professionals from the centers for disease control and prevention and the American heart association. Circulation, 107: 499-511.

Pitsavos, C., D.B. Panagiotakos, N. Tzima, C. Chrysohoou, M. Economou, A. Zampelas and C. Stefanadis, 2005. Adherence to the mediterranean diet is associated with total antioxidant capacity in healthy adults: The ATTICA study. Am. J. Clin. Nutr., 82: 694-699.

Qi, L., J.B. Meigs, S. Liu, J.E. Manson, C. Mantzoros and F.B. Hu, 2006. Dietary fibers and glycemic load, obesity and plasma adiponectin levels in women with type 2 diabetes. Diabetes Care, 29: 1501-1505.

Rana, J.S., T.Y. Li, J.E. Manson and F.B. Hu, 2007. Adiposity compared with physical inactivity and risk of type 2 diabetes in women. Diabetes Care, 30: 53-58.

Ridker, P.M., J.E. Buring, N. Rifai and N.R. Cook, 2007. Development and validation of improved algorithms for the assessment of global cardiovascular risk in women: The reynolds risk score. JAMA, 297: 611-619.

Ridker, P.M., E. Danielson, F.A. Fonseca, J. Genest and A.M.Jr. Gotto *et al*., 2008. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. N. Engl. J. Med., 359: 2195-2207.

Rosenson, R.S., 2010. Lp-PLA(2) and risk of atherosclerotic vascular disease. Lancet, 375: 1498-1500.

Rosin, B.L., 2007. The progression of cardiovascular risk to cardiovascular disease. Rev. Cardiovasc. Med., 8: s3-s8.

Ross, R., 1999. Atherosclerosis: An inflammatory disease. N. Eng. J. Med., 340: 115-126.

Rudez, G., N.A. Janssen, E. Kilinc, F.W. Leebeek and M.E. Gerlofs-Nijland *et al*., 2009. Effects of ambient air pollution on hemostasis and inflammation. Environ. Health Perspect., 117: 995-1001.

Saris, W.H.M., S.N. Blair, M.A. Van Baak, S.B. Eaton and P.S. Davies *et al*., 2003. How much physical activity is enough to prevent unhealthy weight gain? Outcome of the IASO 1st stock conference and consensus statement. Obes. Rev., 4: 101-114.

Shao, B., M.N. Oda, T. Vaisar, F.J. Oram and J.W. Heinecke, 2006. Pathways for oxidation of high-density lipoprotein in human cardiovascular disease. Curr. Opin. Mol. Ther., 8: 198-205.

Simopoulos, A.P., 1991. Health Effects of [omega]3 Polyunsaturated Fatty Acids in Seafoods. In: World Review of Nutrition and Dietetics, Simopoulos, A.P. (Eds.). Vol. 66, Karger, Switzerland, pp: 592.

Steinbrecher, U.P., S. Parthasarathy, D.S. Leake, J.L. Witztum and D. Steinberg, 1984. Modification of low density lipoprotein by endothelial cells involves lipid peroxidation and degradation of low density lipoprotein phospholipids. Proc. Natl. Acad. Sci. USA., 81: 3883-3887.

Steinberg, D., S. Parthasarathy, T.E. Crew, J.C. Khoo and J.L. Witztum, 1989. Beyond cholesterol: Modification of low-density lipoprotein that increase its atherogenecity. N. Engl. J. Med., 320: 915-924.

Steinberg, D. and A. Lewis, 1997. Conner memorial lecture: Oxidative modification of LDL and atherogenesis. Circulation, 95: 1062-1071.

Strasser, B. and B. Pichler, 2004. Diet and physical activity in the treatment of obesity. Wien Med. Wochenschr., 154: 313-319.

Sun, Y.P., B.Q. Zhu, R.E. Sievers, S.A. Glantz and W.W. Parmley, 1994. Metoprolol does not attenuate atherosclerosis in lipid-fed rabbits exposed to environmental tobacco smoke. Circulation, 89: 2260-2265.

Tamagawa, E., N. Bai, K. Morimoto, C. Gray and T. Mui *et al*., 2008. Particulate matter exposure induces persistent lung inflammation and endothelial dysfunction. Am. J. Physiol. Lung Cell Mol. Physiol., 295: L79-L85.

Tanasescu, M., M.F. Leitzmann, E.B. Rimm and F.B. Hu, 2003. Physical activity in relation to cardiovascular disease and total mortality among men with type 2 diabetes. Circulation, 107: 2435-2439.

Thompson, A., P. Gao, L. Orfei, S. Watson and E. Di Angelantonio *et al*., 2010. Lipoprotein-associated phospholipase A(2) and risk of coronary disease, stroke and mortality: Collaborative analysis of 32 prospective studies. Lancet, 375: 1536-1544.

Tracy, R.P., 1998. Inflammation in cardiovascular disease. Circulation, 97: 2000-2002.

Van Gaal, L.F., I.L. Mertens and C.E. De Block, 2006. Mechanisms linking obesity with cardiovascular disease. Nature, 444: 875-880.

Varo, N., J.A. de Lemos, P. Libby, D.A. Morrow and S.A. Murphy *et al*., 2003. Soluble CD40L: Risk prediction after acute coronary syndromes. Circulation, 108: 1049-1052.

Vishnevetsky, D., V.A. Kiyanista and P.J. Gandhi, 2004. CD40 ligand: A novel target in the fight against cardiovascular disease. Ann. Pharmacother., 38: 1500-1508.

WHO, 2008. The World Health Report 2008: Primary Health Care Now More than Ever. World Health Organization, Geneva, Switzerland, pp: 119.

Wei, C., M. Penumetcha, N. Santanam, Y.G. Liu, M. Garelnabi and S. Parthasarathy, 2005. Exercise might favor reverse cholesterol transport and lipoprotein clearance: Potential mechanism for its anti-atherosclerotic effects. Biochim. Biophys. Acta., 1723: 124-127.

White, H., 2010. Editorial: Why inhibition of lipoprotein-associated phospholipase A2 has the potential to improve patient outcomes. Curr. Opin. Cardiol., 25: 299-301.

Williamson, G., D. Barron, K. Shimoi and J. Terao, 2005. *In vitro* biological properties of flavonoid conjugates found *in vivo*. Free Radic. Res., 39: 457-469.

Yla-Herttuala, S., M.E. Rosenfeld, S. Parthasarathy, C.K. Glass, E. Sigal, J.L. Witztum and D. Steinberg, 1990a. Colocalization of 15-lipoxygenase mRNA and protein with epitopes of oxidized low density lipoprotein in macrophage-rich areas of atherosclerotic lesions. PNAS, 87: 6959-6963.

Yla-Herttuala, S., W. Palinski, M.E. Rosenfeld, D. Steinberg and J.L. Witztum, 31990b. Lipoproteins in normal and atherosclerotic aorta. Eur. Heart J., 11: 88-99.

Yla-Herttuala, S., M.E. Rosenfeld, S. Parthasarathy, E. Sigal, T. Sarkioja, J.L. Witztum and D. Steinberg, 1991. Gene expression in macrophage-rich human atherosclerotic lesions: 15-lipoxygenase and acetyl low density lipoprotein receptor messenger RNA colocalize with oxidation specific lipid-protein adducts. J. Clin. Invest., 87: 1146-1152.

Young, I.S., C. McFarlane and J. McEneny, 2003. Oxidative modification of triacylglycerol-rich lipoproteins. Biochem. Soc. Trans., 31: 1062-1065.

Zakynthinos, E. and N. Pappa, 2009. Inflammatory biomarkers in coronary artery disease. J. Cardiol., 53: 317-333.