Review Article

Atherosclerosis and Physical Activity

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Abstract

Atherosclerosis and coronary heart disease have been considered as major health problem worldwide. Abnormalities in lipids and lipoprotein metabolism and impairment of endothelial function have been implicated as the main contributing factors in atherosclerosis and its progression. Physical activity has been recognised as a preventive measure for atherosclerosis.

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Introduction

The clinical presentations of atherosclerosis mainly involve the coronary and carotid arteries, which remain the leading causes of morbidity and mortality in both men and women of all racial groups with Coronary Heart Disease (CHD) the leading cause of death worldwide.[1] The presence of CHD is considered to be a reliable index for more widespread of atherosclerosis. The disease develops slowly over many years in the intima layer of large and medium sized arteries, with devastating manifestations usually after the fourth or fifth decade.[2]

Many factors have been attributed to the aetiology of atherosclerosis; inherited and lifestyle factors contribute to the progression and clinical manifestations. A major contributor to this progression is abnormalities in lipid and lipoprotein metabolism. The association of high concentrations of plasma cholesterol, particularly Low Density Lipoprotein (LDL) cholesterol, and CHD is emphasised by the findings of cholesterol-lowering drug intervention trials.[3-6]

Numerous epidemiological studies have demonstrated an inverse relation between HDL cholesterol levels and the incidence of atherosclerotic CHD.[7] High-Density Lipoprotein (HDL) has both anti-oxidative and anti-inflammatory activities, in addition to their known cardioprotective role in reverse cholesterol transport.[8,9] HDL is considered to be an important marker of CHD risk.[10] Patients with low levels of HDL cholesterol have a significantly increased risk of developing atherosclerotic coronary events.[11-13] Increased HDL cholesterol levels were identified as the most important predictor of a favourable outcome with respect to a reduction in myocardial infarction rates after lipid-lowering therapy.[14] The association of elevated HDL cholesterol levels with protection against CHD has been attributed to indicate the efficiency of reverse cholesterol transport involved in removing cholesterol from the atheroma.[15]

Several studies assessed the relationships between TriGlyceride (TG), TG-Rich Lipoproteins (TG-RL) and the development of atherosclerosis. The link between TG and CHD was established in the1950s; Albrink and Man reported that fasting TG levels were increased among patients with CHD.[16] In addition, Hokanson and Austin concluded on the basis of combined data from prospective studies, that serum TG concentration is a risk factor for cardiovascular disease for both men and women in the general population, independent of high-density lipoprotein (HDL) cholesterol.[17] Moreover, in a prospective study, Jeppesen et al. have shown that TG concentrations independently predict CHD in men.[18]

Subsequently, a large number of studies have shown a relationship between fasting TG concentrations and CHD, although, in multivariate analysis TG tends to be eliminated as an independent CHD risk factor by HDL cholesterol.[19] In addition, there has been increasing interest in TG-RL subclasses in the pathogenesis of atherosclerosis and CHD.[20] Koren et al. already demonstrated that some TG-RL particles represent a risk for CHD.[21] Another meta-analysis concluded that even after adjustment for HDL cholesterol and other risk factors, plasma TG is still an independent risk factor for cardiovascular disease.[22-25] Fasting TG concentrations alone was considered a poor marker of TG metabolism.[26,27]

Effectively, the close relationship linking high TG concentrations with potentially atherogenic factors such as Intermediate Density Lipoprotein (IDL), small dense LDL and increased cholesteryl ester exchange may affect its predictive power in CHD risk.[28] In the context of 24-hour TG metabolism, the fasting TG concentration could be considered spurious as it is considered an unstressed, equilibrated state that is not representative of the dynamic metabolic state present for most of the day. As human beings consume meals regularly during the waking hours, plasma TG concentrations are above fasting levels for perhaps three-quarters of the day.[29]

Furthermore, these postprandial TG concentrations are not necessarily reflected by fasting TG concentrations. Individuals with

similar fasting TG concentrations exhibit markedly varying plasma TG responses to an oral fat load.[30-32] Moreover, a raised non-fasting concentration of TG was found as an independent risk factor for mortality from CHD, cardiovascular disease and all cause mortality amongst middle-aged Norwegian women.[33] Another prospective study concluded that non-fasting TG levels appear to be a strong and independent predictor of future myocardial infarction. [34]

Thus, the apparent weak association between TG concentrations and CHD risk may theoretically be strengthened when TG concentrations in the postprandial state are considered. Several case-control studies have indicated postprandial lipaemia to be a significant risk factor for CHD.[35-37]

In addition to lipid and lipoprotein metabolism, abnormalities in endothelial function play a central role in the development of atherosclerosis and CHD.[38, 39] This phenotype of endothelial dysfunction has been studied using numerous techniques including measurements of Flow-Mediated (endothelium-dependent) Vasodilatation (FMD), using high-resolution ultrasound.[40] In addition to gold standard intra-arterial infusion of vasoactive agents with forearm blood flow measured by venous occlusion plethysmography.[41]

Several studies have suggested abnormalities of endothelial function following ingestion of a high-fat meal. Vogel et al. reported impaired FMD under these circumstances, partly via transient accumulation of TG-RL.[42] Others have shown that transient hypertriglyceridaemia decreased vascular reactivity in the brachial artery in young, healthy men without risk factors for CHD, affecting both endothelium-dependent and endothelium-independent mechanisms.[43] Hypercholesterolaemia may impair endothelial function via increases in endothelial production of superoxide and possibly other oxygen free radicals that react with and "quench" nitric oxide.[44, 45]

Physical Activity in Prevention of Atherosclerosis

The link between physical activity and CHD was first established in the early 1950s and since this time population studies have consistently found high levels of physical activity to be associated with reduced risk of CHD morbidity and mortality.[46, 47] Reports evaluating the results of several populations studies have concluded that inactive individuals are about twice as likely to develop CHD as their active counterparts.[48-53]

The sedentary lifestyle prevalence is rising rapidly. The level of risk associated with sedentary lifestyle is comparable to that conferred by hypertension, smoking or high serum cholesterol concentrations and on the basis of this evidence the American Heart Association has highlighted physical inactivity as an independent risk factor for cardiovascular disease.[54] Some studies have shown that lifestyle modification and physical activity intervention are as effective as a structured exercise program in improving physical activity, cardiorespiratory fitness, and blood pressure.[55]

An inverse association between physical fitness and CHD morbidity and mortality has similarly been reported. Increases in level of physical activity or fitness are associated with reduction in CHD, suggesting that unfit or sedentary individuals can improve their risk profile by starting an exercise program.[56] In both men and women, there is an inverse relation between the level of physical activity and the incidence of cardiovascular disease, and this relationship persists after control for other risk factors.[57, 58] Paffenbarger et al. reported that taking up moderately vigorous exercise resulted in a substantial reduction in mortality from all causes by 23% and from CHD by 41% compared with sedentary classmates.[59] Maintaining or increasing physical activity level in late middle age was associated with a reduction in mortality rates, and light activities appeared to be sufficient to produce this benefit in older men.[60-62]

Among patients with established cardiovascular disease, mortality is lower among those who participate in an exercise program than among those who do not. [63] Lemaitre et al. have shown that postmenopausal women in such a program had reduced the risk of myocardial infarction by 50% with modest leisure-time energy expenditures, equivalent to 30 to 45 minutes of walking for exercise three times a week.[64] Furthermore, Wannmethee et al. based on data from the British Regional Heart Study concluded that light or moderate activity (e.g. moderate gardening) in men with established CHD is associated with lower risk of all-cause mortality.[65] Participating in regular physical activity more than three days per week resulted in fewer coronary risk factors; even those who engaged in physical activity once a week had fewer risk factors than sedentary individuals.[66]

It has been shown that the beneficial effects of exercise (i.e., higher concentrations of HDL cholesterol and lower adiposity, triglyceride concentrations, ratio of total cholesterol to HDL cholesterol, and estimated 10-year risk of coronary heart disease) appear to increase with distances run of up to at least 80 km per week.[67] Recognising the potential importance of regular physical activity in the prevention of CHD, the American College of Sports Medicine and the Centres for Disease Control and Prevention recommended 30 minutes or more of moderate-intensity physical activity on most days of the week and these recommendations were emphasized in 2006.[68, 69]

The mechanisms by which physical activity/physical fitness

attenuate CHD risk have not been fully elucidated, but are likely to involve changes in lipid and lipoprotein metabolism. Individuals who regularly exercise possess lipoprotein profiles consistent with a low risk of CHD, and typically having HDL cholesterol concentrations that are 20-30% higher than untrained individuals as well as lower TG concentrations in the fasting state.[70] In particular, there appears to be a dose-response relationship between the amount of exercise performed and HDL cholesterol concentration.[71, 72]

Longitudinal training interventions often report increases in HDL cholesterol.[71,72] Given the relationship between TG metabolism and HDL cholesterol concentrations, it is probable that elevated HDL cholesterol concentrations are a consequence of efficient metabolism of TG-RL.[73] Indeed, some studies suggest that even a single session of moderate- to long-duration exercise can reduce blood pressure, glucose, and TG and can increase HDL cholesterol concentrations.[74-78] Recently, a meta analysis have confirmed that regular aerobic exercise modestly increases HDL level with a minimum exercise volume required for a significant increase in HDL level and exercise duration per session was the most important element of an exercise prescription and exercise was more effective in subjects with initially high total cholesterol levels or low body mass index.[79]

Nitric Oxide (NO) is recognised as one potential mediator of some of the vascular benefits derived from regular exercise.[80] Vasodilatation in active muscle promotes a pressure gradient and thus increases blood flow which stimulates NO production from upstream arteries.[81] NO mediated dilatation of feed arteries can therefore permit increased microvascular flow without reduction in muscle perfusion pressure. With regular exercise it appears that there are adaptations in this system that may be partly responsible for the reduction in cardiovascular risk associated with trained state. The mechanisms responsible for these effects have been elucidated in animal models and cell-culture systems.[82]

Physical exercise increases coronary blood flow, resulting in increased shear stress on the surface of the endothelium. Endothelial cells respond to short-term increases in shear stress by producing vasodilator compounds such as prostacyclin and NO. Sustained increases in shear stress illicit an adaptive response in endothelial cells that is manifested, in part, by increased expression of endothelial NO synthase.

Predictably, endothelial function in animals that perform regular exercise is improved as a result of increased endothelial NO production and is better than that in animals who do not exercise. In experimental animals using dogs, coronary blood flow was increased by a 10-day exercise program.[83] As acetylcholine-stimulated NO release was markedly enhanced in large coronary arteries and microvessels from hearts of the exercised dogs compared with hearts from control dogs, the authors concluded that exercise via prolonged increases in shear stress resulted in the observed increased nitric oxide synthase gene expression in the coronary artery.[83]

Physical inactivity is a major risk factor for CHD, and exercise-training programs can improve endothelium-dependent vasodilatation both in epicardial coronary vessels and in resistance vessels in patients with CHD.[84] Moreover, regular exercise improved both basal endothelial NO production and agonist mediated endothelium-dependent vasodilatation of the skeletal muscle vasculature in patients with congestive heart failure.[85] In addition, Hornig et al. have shown that physical training restores FMD in patients with chronic heart failure, possibly by enhanced endothelial release of NO.[86]

Regular physical exercise has been shown to improve endothelial function in experimental animals and in healthy young men.[87, 88] Higashi et al. had shown that long-term physical exercise improved endothelium-dependent vasorelaxation through an increase in the release of NO in normotensive and hypertensive subjects.[89] Exercise training for only four weeks has been shown to increase basal nitric oxide production in hypercholesterolaemic patients, independent of lipid profile modification.[90] A 12-week moderate intensity exercise program improved endothelium-dependent vasorelaxation with acetylcholine but not endothelium-independent vasorelaxation with isosorbide dinitrate and this moderate-intensity exercise fits the index of exercise training that is recommended from the general viewpoint of prevention of cardiovascular disease.[91]

In addition, a single session of moderate intensity exercise has been shown to improve endothelial function and attenuate the effect of ingestion of high fat meal in lean and obese subjects.[92] However, these findings were not conclusive in patients with type 2 diabetes.[93]

In summary; lipids, lipoprotein metabolism and endothelial function are the major contributing factors of atherosclerosis. While these studies reveal the potential for exercise to influence lipoprotein metabolism and endothelial function, they do not provide enough information about the mechanisms responsible for these changes.

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