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Scientific Update™

Multifactorial Approach to the Treatment of Cardiovascular Disease

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The etiology of cardiovascular disease, in particular coronary artery disease, is multifactorial. Among the many risk factors well recognized by clinicians and patients alike, diabetes – or, more precisely, glucose intolerance – is perhaps the least appreciated with respect to its frequency and importance. In addition, glucose and lipid intolerance interact synergistically to cause an unfortunate combination of adverse metabolic and vascular abnormalities that leads to a markedly increased risk of atherosclerosis.

Impaired glucose tolerance and cardiovascular complications

The prevalence of diabetes mellitus is 5% in the North American population, but it is >10% in those aged 65-75 years. Only half of patients with diabetes are diagnosed, resulting in a 20% prevalence in this age group. Overt diabetes, characterized as elevations in fasting blood sugar, leads to a two-fold increase in the risk of developing cardiovascular disease. However, there is an important continuum between impaired glucose tolerance and overt diabetes, caused by both genetic and environmental factors. It is characterized by insulin resistance and elevated blood sugar 2 hours after a standard meal, which is associated with hyperinsulinemia. This pre-diabetic state of glucose intolerance is a definite risk factor for macrovascular complications, even though it is not a risk factor for the microvascular complications well known in overt diabetes. This risk from impaired glucose tolerance (IGT) is multiplicative with other risks such as lipid abnormalities and smoking.

Many epidemiologic studies, such as the Honolulu Heart Study, have shown that impaired glucose tolerance is an independent risk factor for coronary artery disease (CAD) over a 12-year period.[1] They have also shown that other complications – for example, sudden cardiac death – progressively increase with elevated blood sugar levels. The BEDFORD study of patients with IGT showed a two-fold increase of death in males but a three- to four-fold increase in females, indicating that the normal protection from coronary disease that premenopausal females enjoy is totally wiped out by the presence of glucose intolerance.[2] Hemoglobin A_1C levels also reflect this increased risk for coronary disease.

In an important study, Després et al from Quebec identified increased insulin levels as a risk factor for CAD and with it an association between hyperinsulinemia and dyslipidemia.[3] This association has been somewhat unfortunately termed *syndrome X*; it is not to be confused with the controversial syndrome of microvascular angina (also known as syndrome X), which is chest pain in people with normal coronary arteries. The metabolic syndrome X includes abdominal obesity, insulin resistance, and dyslipidemia: elevated triglycerides, decreased high-density lipoprotein (HDL), and changes in low-density lipoprotein (LDL) subfractions without, necessarily, elevations in overall LDL. Glucose tolerance is also impaired in syndrome X.

When does the clock start ticking with respect to the development of atherosclerosis in diabetes? Epidemiologic studies and basic research imply that the risk of atheroscle-

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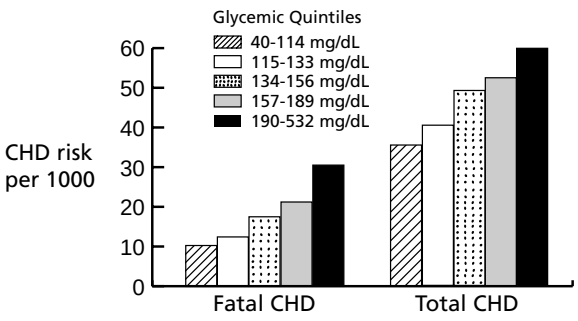
Figure 1: Honolulu Heart Study



12-year age-adjusted incidence of fatal CHD (coronary heart disease) and total CHD by casual one-hour serum glucose
P < .001 for fatal CHD comparing quintile 1 to 5
P < .01 for total CHD comparing quintile 1 to 5
N = 8,006 males
Adapted from Donahue, RP

rosis and vascular events begins to increase as early as 5 years prior to the diagnosis of overt diabetes mellitus (see figure 1). A 2-hour PC glucose level of 7.8 makes evident the risk of microvascular complications. A lower level of 7.0 on two occasions indicates the risk of subsequent development of overt diabetes mellitus. With 2-hour glucose levels as low as 6 mmol/L, there appears to be an increased risk of macrovascular complications. Thus, a rising blood glucose level, even within the so-called normal range, is a continuous risk factor for CAD, much as blood pressure or cholesterol elevations are.

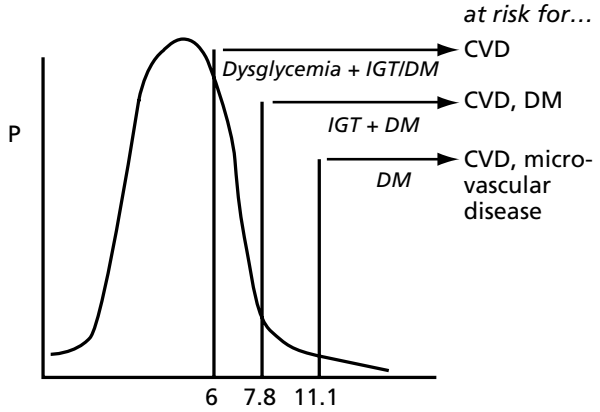
In the hope of preventing the progression from IGT to overt diabetes mellitus, the STOP Diabetes study is currently being conducted in Canada, Scandinavia, and Germany. It involves treating patients with impaired glucose tolerance with acarbose, an alpha-glucosidase inhibitor.

Glucose and lipid disorders in the postprandial phase

The postprandial state lasts up to 8 hours after the last meal, which covers much of the daytime for most individuals. Insulin is required to metabolize very-low-density lipoprotein (VLDL) and to help dispose of VLDL remnants without their being incorporated into endothelial and subendothelial tissues. A relative deficiency of insulin, therefore, can lead to increases in triglyceride concentrations and decreases in HDL; it can also cause changes in lipoprotein composition resulting in an increase in small dense LDL particles, which are particularly atherogenic. The hyperinsulinemia and hyperglycemia of impaired glucose tolerance produce several effects – increased oxidative stress on endothelial cells, proliferation of adhesion molecules, delays in LDL clearance, and increased risk of glycosylation and oxidation of LDL – all of which lead to endothelial dysfunction.

Such abnormalities are reflected in structural disturbances in blood vessels – for example, increases in the intima-to-media ratio. Just what independent risks arise from hypertriglyceridemia in non-diabetics is controversial. In diabetics, however, there is excellent evidence that triglycerides are indeed independent risk factors for CAD and that postprandial levels of glucose, as well as triglycerides, are more powerful predictors of CAD risk than fasting glucose and triglyceride levels. Patients can reduce triglyceride levels through weight loss, exercise, isocaloric dietary changes, or treatment of the diabetes with acarbose or metformin, as well as by using fibrate derivatives and statins (i.e., HMG-CoA reductase inhibitors). One such statin – cerivastatin – has been shown to decrease LDL cholestorol by 20-30% and triglycerides by 25%, and to increase HDL by 5-10%.

Figure 2: Glucose levels and chronic disease.



IGT = Impaired Glucose Tolerance
DM = Diabetes Mellitus
CVD = Coronary/Vascular Disease
P is prevalence of fasting glucose levels in the population. Note the much larger number of patients with glucose levels of 6 to 7.8 mmol/L at risk for macrovascular disease, than those with frank diabetes at >7.8 mmol/L.

Human genetics of atherosclerosis and lipoprotein disorders

Only 20% of patients with CAD have elevated cholesterol, but 80% have an inherited disease of lipoprotein metabolism that is linked to CAD. Defects in any of the genes that code for enzyme proteins, receptor proteins, and apolipoproteins, which directly interact with lipid particles, can cause abnormalities in lipid metabolism.

Common lipid disorders can confer up to a threefold increase in atherosclerosis. These disorders are detected by routine tests. Perhaps the most important test is for the atherogenic lipoprotein profile (ALP): normal or slightly elevated total cholesterol, abnormal LDL composition, and an increased quantity of highly atherogenic small, dense LDL particles. A positive profile is characterized by hyperinsulinemia, slight hypertriglyceridemia, and decreased HDL. Small LDL particles rapidly enter into vascular walls and are susceptible to oxidative stress due to a decrease in vitamin E levels. This condition responds to diet and antioxidants, and it can also be successfully treated with fibrates and statins.

In a relatively common disorder, occurring in some 2% of the population, there is an abnormal level of a lipoprotein known as Lp(a). The genetic defect for this has been identified. The extent of the disorder is difficult to measure, but up to 50% of first-degree relatives might be affected, and there is an associated increase in the risk of CAD and its complications.

Familial heterozygous hypercholesterolemia is associated with a heterozygous condition leading to increases in cholesterol, and it is present in 1 in 500 individuals. It can be caused by a defective LDL receptor, or by a mutation in the apo B protein that does not allow the lipid-protein complex to bind to the LDL receptor. The consequences of these defects are similar: excess LDL in circulation and in vessel walls. So far, studies show that the risks can be reduced with statin therapy, suggesting that this benefit is a class effect. These studies include trials in secondary prevention (4S, PLAC, REGRESS, CARE)[4-6] and primary prevention (WOSCOP[7]). Although LDL reduction, whether used in primary or secondary prevention, is beneficial for all patients with elevated cholesterol, LDL elevation is only one of several metabolic conditions contributing to the risks of CAD.

Familial combined hyperlipidemia is a complex disorder whose cause is multifactorial and not well understood. It causes elevations of both cholesterol and triglycerides, marked variation in an individual's lipid values over short periods, and a four-fold increased risk of CAD.

The final, more unusual, group of disorders is characterized by marked reductions in HDL concentration (<25 mg/dL). These are the hypoalphalipoproteinemias. Experimental animals with these disorders have been successfully treated with gene therapy.

Lipid abnormalities are very common and frequently inherited; therefore, the families of affected individuals are at risk. However, they can be treated, with the appropriate treatment focused on the particular defect.

Effects of statins and calcium channel blockers on progression of atherosclerosis

There is clear-cut evidence (e.g., the 4S and CARE studies) that lipid-lowering therapy reduces clinical events and mortality in patients with CAD and hyperlipidemia. Angiographic studies of lipid lowering with statins show that it prevents the progression of extant coronary artery lesions or the formation of new ones. A summary of all these studies indicates that the effect of lipid-lowering therapy, and possibly other therapies, on the structure, morphology, and function of the blood vessel wall are likely to predict ultimate clinical end-points in these studies. Thus, such indirect effects as angiographic lesion size or vessel morphology by intracoronary ultrasound can continue to be used as surrogate end-points in evaluation of therapies whose ultimate aim is to reduce morbidity and mortality from CAD.

In angiographic trials, progression is invariably reduced by statins, but regression rarely occurs; in most patients, some lesions still progress. This suggests that statins are not sufficiently powerful to induce regression of atherosclerosis and that there is room for improvement, possibly with additional therapies.

Although the evidence for prevention of progression or new lesion formation by calcium channel blockers (CCBs) is controversial, some studies suggest that these drugs might reduce the number of new lesions formed, and the evidence is even stronger in cholesterol-fed animal models. The REGRESS study showed that pravastatin prevented the progression of coronary lesions. In a very interesting retrospective analysis of this study, patients who received pravastatin combined with CCBs were compared with those who received pravastatin but no CCBs. There were no differences between these two groups in patient characteristics, extent of angiographic lesions, or degree of lipid lowering. Nevertheless, in the group assigned to pravastatin which also took CCBs, there were 50% fewer new lesions than in the group that received pravastatin alone. Nifedipine appeared to be

superior to diltiazem in this potentially beneficial combination. It is important to emphasize that this was a subgroup retrospective analysis; nevertheless, the finding is sufficiently exciting to justify a randomized controlled trial of a combination of statins and CCBs.

Endothelial dysfunction in atherosclerosis

Morphologic and biochemical abnormalities occur in CAD, including both increases in the ultrastructure (intima/media ratio) and the function (capacity for vasodilatation) of coronary and other arteries. Experimental evidence suggests that CCBs can beneficially affect both structure and function of such diseased vessels. It is more clearly evident, however, that statins reverse the ultrastructural changes thought to characterize the early stages of CAD, but this reversal takes more than two years; in contrast, statins beneficially alter the metabolic abnormalities of diseased endothelium in as little as six months.

A good surrogate marker for endothelial dysfunction is the occurrence of vasoconstriction – rather than the vasodilatation that normally occurs – in response to acetylcholine challenge. In preliminary work, CCBs have been shown to acutely reverse exercise-induced vasoconstriction in hypertensive patients.

The ENCORE trials

In view of the suggestive evidence for CCBs and the very good evidence for statin drugs, the ENCORE (Evaluation of Nifedipine and Cerivastatin On Recovery of Endothelial dysfunction) trial now under way will assess the potential benefit of combining a CCB (nifedipine) with a statin (cerivastatin) to prevent worsening of CAD following percutaneous transluminal coronary angiography. Cerivastatin is a new, synthetic, potent HMG-CoA reductase inhibitor that effectively reduces LDL-C and triglycerides.

The ENCORE trial has randomized 400 patients to either placebo, nifedipine GITS (30-60 mg/day), cerivastatin (0.4 mg/day), or a combination of the two. Patients will be evaluated at baseline and at six months with quantitative coronary angiography and vasodilation response to infused acetylcholine.

A companion study – ENCORE II – will compare results for patients taking cerivastatin alone with those for patients treated with a combination of cerivastatin followed by nifedipine. This time the evaluation will be over a two-year period; results of intravascular ultrasound and quantitative coronary angiography will determine the end points.

The two ENCORE trials will, therefore, examine the hypothesis that the combination of CCBs and lipid-lowering therapy has a better effect on endothelial function and structure than either therapy alone. In addition, the studies will allow a comparison of quantitative coronary angiography and intravascular ultrasound as ways to measure the effects of therapies to prevent or to ameliorate CAD.

Conclusion

Endothelium is an important modulator of cardiovascular health and disease. Endothelial dysfunction is a common link among various risk factors – for example, diabetes or hyperlipidemia and atherosclerosis. Thus endothelial dysfunction is now coming into focus as a therapeutic target, with lipid-lowering already identified as beneficial. New therapeutic options in the treatment of endothelial dysfunction will include CCBs and angiotensin-converting enzyme inhibitors.

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