THE ROLE OF HYPERTRIGLYCERIDEMIA AS A CORONARY RISK FACTOR

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INTRODUCTION

For the past two decades, age-adjusted mortality rates for coronary artery disease have been steadily declining in the United States.1 While this encouraging decline can be attributed to continued improvements in diagnostic capabilities, medical therapy, interventional cardiology and coronary artery bypass surgery, the precise cause of this encouraging decline is complex.

Multiple theories have been proposed to explain the initiation and progression of atherosclerosis, yet researchers have yet to identify a unifying hypothesis that explains all aspects of coronary artery disease. The initial lipid hypothesis proposed more than 100 years ago was based on the premise that dyslipidemia is central to the process of atherosclerosis. The corollary of this hypothesis is that optimization of the lipid profile will reduce the risk of a future coronary event. While initially controversial, an overwhelming body of evidence accumulated from large-scale genetic, epidemiologic, pathologic and clinical studies has confirmed the primary role of dyslipidemia in coronary and peripheral atherosclerosis. Even so, the utilization of total cholesterol as both a marker for risk and target for therapy has significant limitations in individual patients.

There is considerable overlap in patient cholesterol levels regardless of documented coronary artery disease (Figure 1), and many clinicians are using lipid subfractions to enhance their ability to predict a patient's risk of experiencing a future coronary event. Cholesterol is carried in lipoproteins, which are associated with a variable impact on coronary risk (Figure 2): low-density lipoprotein (LDL) and lipoprotein (a) are clearly atherogenic, whereas elevated levels of high-density lipoprotein (HDL) are associated with reduced cardiovascular risk. While chylomicrons are considered a neutral cardiovascular risk despite dramatically elevated cholesterol and triglycerides, hyperchylomicronemia is associated with a significant risk for necrotizing pancreatitis.

The role of elevated triglyceride levels as an independent risk factor for coronary heart disease has been controversial. An increasing body of research has confirmed that subjects with hypertriglyceridemia are at risk for coronary heart disease, and trials performed with pharmacologic agents that directly affect hypertriglyceridemia have demonstrated clinical benefit in some but not all studies.

This review will discuss the epidemiologic relationships between elevated triglycerides and coronary risk, potential atherogenic mechanisms and recent clinical trials.

HYPERTRIGLYCERIDEMIA AND CORONARY ARTERY DISEASE

LDL is considered to be the major atherogenic particle and has a strong correlation with increased coronary risk. It carries approximately 70% of circulating cholesterol, and clinical trials using pharmacologic agents that lower LDL cholesterol (e.g. statins or bile acid resins) have demonstrated reduced cardiovascular mortality. The role of triglyceride-rich lipoproteins as an independent risk factor, however, is less clear. Hypertriglyceridemia is associated with a number of prothrombotic factors such as hyperfibrinogenemia, elevated plasminogen activacor inhibi-

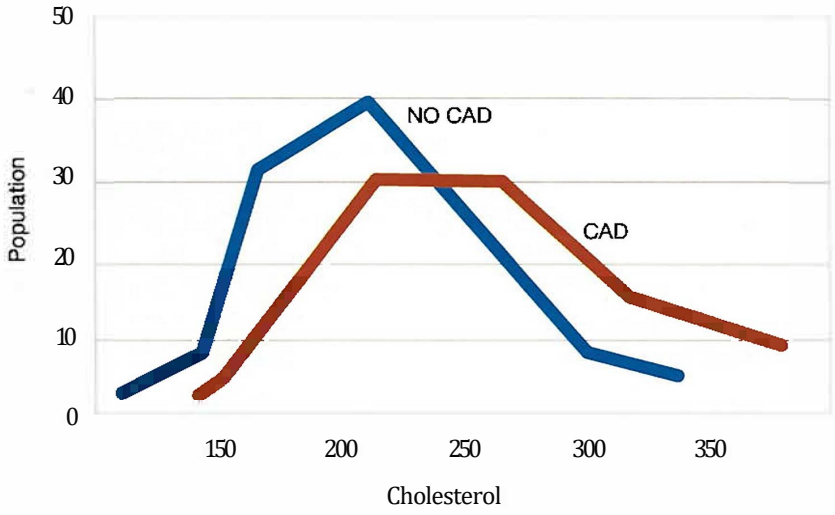

Figure 1. Total Cholesterol and CAD

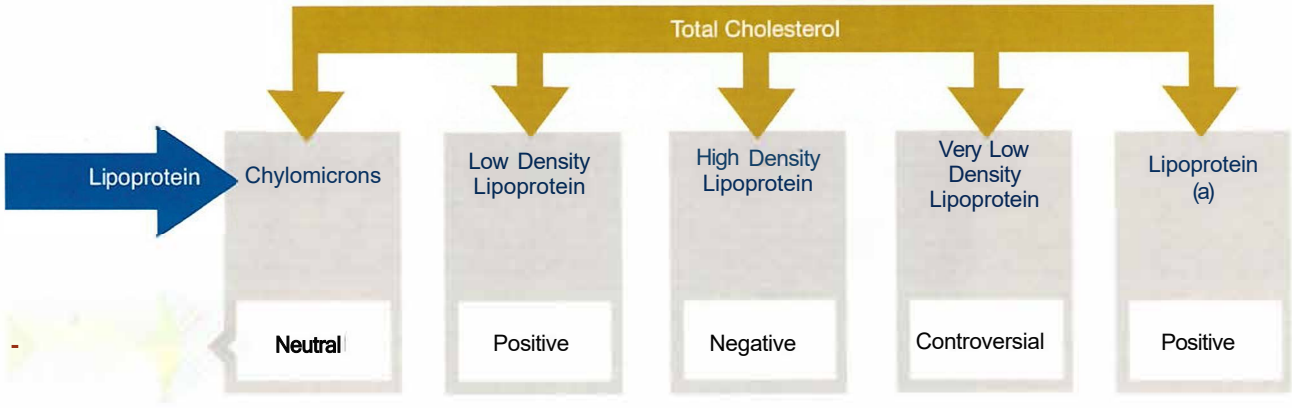

Figure 2. Coronary Risk and Upoproteins

tor and increased platelet aggregation, and early epidemiologic studies demonstrated a positive statistical relationship between elevated triglycerides and coronary artery disease. Yet subjects with hypertriglyceridemia frequently exhibit a variety of other risk factors such as diabetes, obesity, sedentary lifestyle and low H D L cholesterol levels.

Follow-up multivariate analysis that controlled for concomicam risk factors appeared co eliminate the excess risk previously attributed to hypercriglyceridemia. For example, data from the Lipid Research Clinic follow-up study demonscrared that elevated triglycerides were significantly correlated with coronary artery disease mortality in both men and women over a 10-year observation, while follow-up multivariate analysis determined that the relationship was not statistically significant. Since the trial was enriched in dyslipidemic subjects, however, the results may not be applicable to the general population. Additionally, the validity of multivariate analysis has been questioned in determining the relationship between lipoprotein parcicles chat are metabolically interrelated, such as H D L and triglyceride-rich particles.

Recent large-scale meta analyses utilizing sophisticated statistical cechniques have implicated a connection between hyperrriglyceridemia and coronary risk independent of H D L cholesterol in both men and women.2 Criteria for inclusion in the analysis required that the clinical trials employed a prospeccive design (to insure rhac the elevated triglycerides preceded the onset of disease), utilized only fasting triglyceride determinations and employed population-based samples to compare to the general populace. The 17 clinical trials that met these selection criteria included 46,413 men who experienced a total of 2445 cardiovascular events over an 8.5 year evaluation period. Researchers also evaluated five studies that included 10,864 women experiencing a total of 439 cardiovascular events over 11.4 years. Univariate analysis demonstrated a 32% increase in risk of coronary disease with the presence of elevated triglycerides. Following adjustment for H D L cholesterol levels, che relacive risk was reduced as expected but scill demonstrated a statistically significant excess cardiovascular risk associated with hypemiglyceridemia of 14% in men and 37% in women.

The ambiguity of the role elevated triglycerides play in the pathogenesis of atherosclerosis is underscored by the fact chat triglycerides are generally not a major component of atherosclerotic plaque. Triglyceride-rich particles are highly heterogeneous and may exhibit differing impacts on cardiovascular risk. Additionally, since lipid profiles are generally measured in the fasting state to avoid inclusion of chylomicrons and partially metabolized remnant particles, the pathologic impact o ftriglyceride-rich particles may be underescimaced since humans frequently exist in the postprandial state. Researchers are focusing on the role of potentially acherogenic triglyceride-rich remnant particles chat remain after ingesting a fatty meal (postprandial lipemia) (Figure 3). Remnant particles are cytotoxic and damage the endothelial lining of the blood vessel;[3] they also rapidly transverse the endothelial barrier for involvement in the monocyte-macrophage system - an initial step in atherosclerosis.

Elevated triglycerides also mark the presence of small, dense L D L particles. Clinically, L D L cholesterol levels are generally not measured directly, nor do they indicate che number of particles that may impact atherosclerotic risk (Figure 4). L D L exists in a variety of subgroups based on size, density and cholesterol content, and small, dense L D L particles are associated with increased cardiovascular risk. This increased risk is multifaccorial and related co increased susceptibility to oxidation, endothelial cytotoxicity and an enhanced ability to traverse the endothelial barrier. While hypemiglyceridemia is a marker for the presence of small, dense L D L (type B), reduced triglyceride levels are associated with a larger, potentially less atherogenic (type

A) form of LDL (Figure 5). Small, dense LDL particles are more common in people with diabetes, known coronary disease, obesity and certain forms of hypertension, but like hypemiglyceridemia, its impact on atherosclermic risk is ambiguous.

Using non-HDL cholesterol - all Apo B-containing particles (LDL and VLDL) - as a marker for coronary risk partially circumvents problems associated with hypertriglyceridemia alone as it is felt to quantify the level of circulating atherogenic lipoproteins.

CLINICAL TRIALS

Epidemiologic and observational studies are effective at generating hypotheses bur do not necessarily prove a causal relationship; properly designed prospective placebo-controlled trials are necessary to determine the efficacy of any clinical intervention. The role of hypertriglyceridemia in atherosclerosis could be tested only by hygienic or pharmacologic interventions char have an isolated effect on the level of circulating triglyceride-rich lipoproteins. While all currently available lipid-lowering therapies affect many different lipid subfractions to varying degrees, they can be a categorized as having a predominant effect on either LDL (e.g. statins or bile acid sequesrrants) or triglycerides. The major triglyceride-lowering drugs have differing mechanism of actions: Nicorinic acid and fish oils rich in omega-3 fatty acids reduce the hepatic production of triglyceride-rich particles, while fibric acid derivatives increase cacabolism.

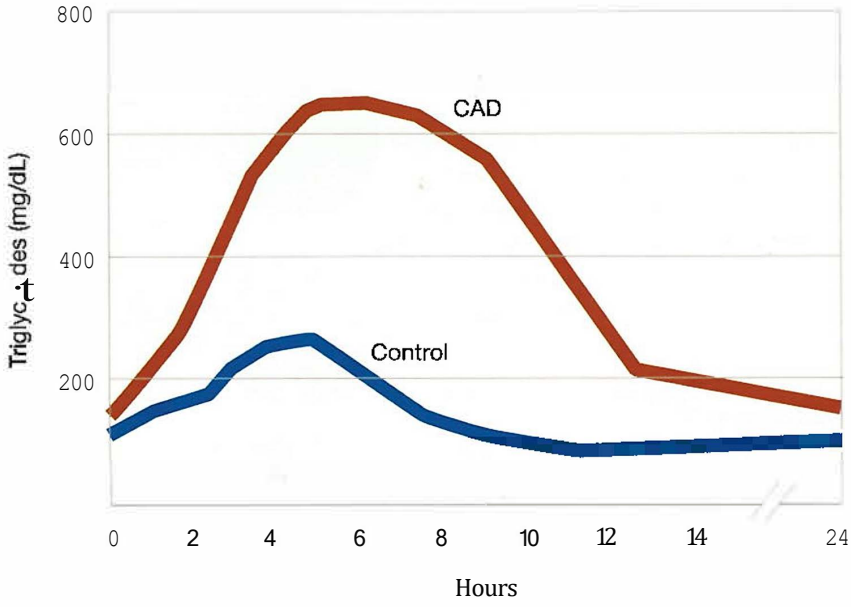

Figure 3. Postprandial Lipemia and Coronary Artery Disease

Fibric acid derivatives were initially demonstrated to reduce cardiovascular mortality in the Helsinki Heart Study.4 Total mortality was not reduced, however, and the absolute reduction in cardiovascular morbidity and mortality was modest. The predominant lipid phenotype in this trial was elevated LDL (Fredrickson IIA), which would not be the ideal choice for fibric acid therapy. In the relatively small subgroup of individuals with hypemiglyceridemia, gemfibrozil demonstrated a significant reduction in cardiovascular events (70% of the total benefit); however, prospective clinical trials are needed for validation.

The Veteran's Administration High-Density Lipoprocein Intervention Trial (VA-HIT) was a secondary prevention trial with more than 2,000 subjects selected on the basis of low HDL cholesterol.5 Gemfibrozil dramatically lowered triglyceride levels by 37%, resulted in a small (7%) but statistically significant increase in HDL cholesterol levels, and significantly reduced cardiovascular mortality despite the fact that LDL was not reduced. Gemfibrozil also significantly reduced event rates in the high-risk diabetic subgroup chat was analyzed. Diabetic dyslipidemia is frequently associated with the lipid triad (elevated triglycerides, low HDL and dense LDL). Since fibric acid therapy appeared to be an ideal therapy for this subgroup, these results prompted the

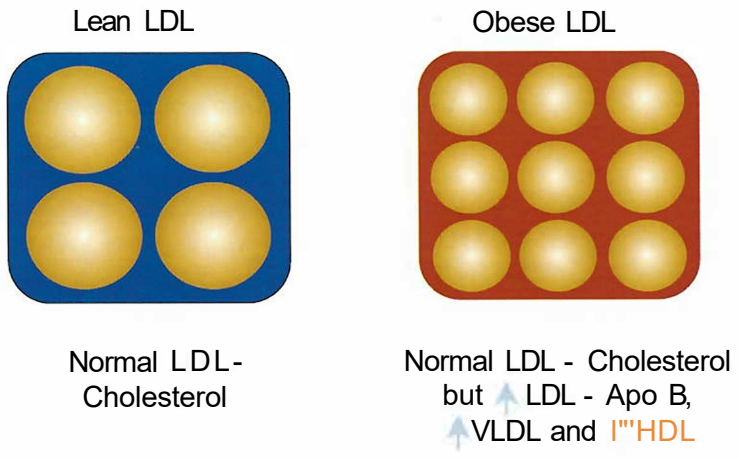

Figure 4. LDL Particle Size in Lean and Obese Patients

initiation of a large-scale trial of fenofibrate in diabetic subjects.

The Fenofibrace Intervention and Event Lowering in Diabetes trial (FIELD) was designed to evaluate the effect of fenofibrate therapy in 9,795 type II diabetic subjects over a five-year trial,6 with the primary end point being fatal and nonfatal myocardial infarction. Fenofibrate improved microvascular complications but reduced che primary end point by only 11%, which was not statistically significant. The disappointing resulrs may be partially explained by an increased use of statin therapy in the placebo group.

Nicocinic acid is a versatile hypolipidemic agent chat beneficially airers all lipid subfractions, including lipoprotein a. It acts primarily by decreasing hepatic production ofVery Low-Density Lipoproceins, although it may also reduce triglycerides by up to 50%, significandy reduce LDL and elevate HDL. The widespread use of nicocinic acid has been limited by a variety of side effects chat range from troublesome (flushing, pruricus, worsening of glucose tolerance) to life-threatening (fatal hepatic necrosis). Nicotinic acid was demonstrated to reduce cardiovascular mortality in the Coronary Drug Project and demonstrated a reduction in decreased total mortality in a long-term continuation of the trial.7 Additionally, nicotinic acid has been combined with statin therapy in mixed dyslipidemia and has proven to be effective in angiographic repression studies.

CONCLUSIONS

Dyslipidemia is a proven causal factor 'In the initiation and progression of vascular disease. Low-density lipoprotein is the major atherogenic particle, and statin therapy is proven to be effective across the spectrum of atherosclerosis. The quantitative role of triglyceride-rich particles as an independent cardiovascular risk factor remains controversial due to significant limitations in the ability to optimize triglycerides without altering

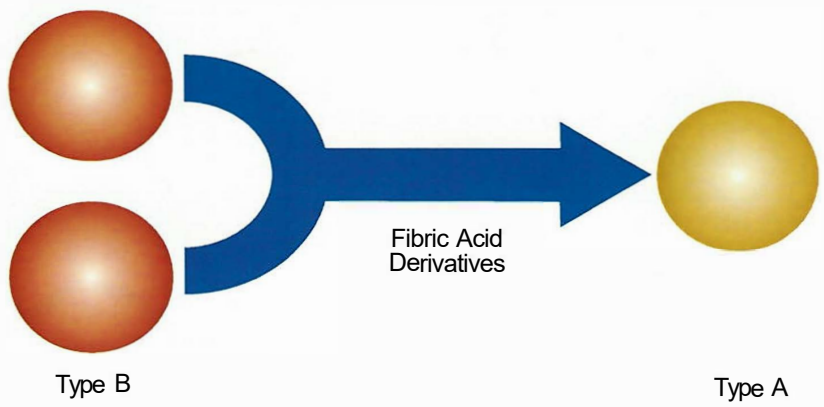

Figure 5. LDL Particle Size and Fibric Acid Therapy

increasing body ot data suggests that hypertriglyceridemia is a significant risk for coronary artery disease. At the very least, elevated triglycerides identify subjects at risk for vascular events. Clinical trials testing pharmacologic agents chat lower triglycerides and raise HDL have demonstrated clinical benefit in some but not all cases. Intensive hygienic measures involving exercise and weight loss may significandy improve triglyceride and HDL levels and should be the cornerstone of therapy. Triglyceride-lowering agents may be employed as monotherapy or in combination with other agents in selected patients with mixed dyslipidemia.

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