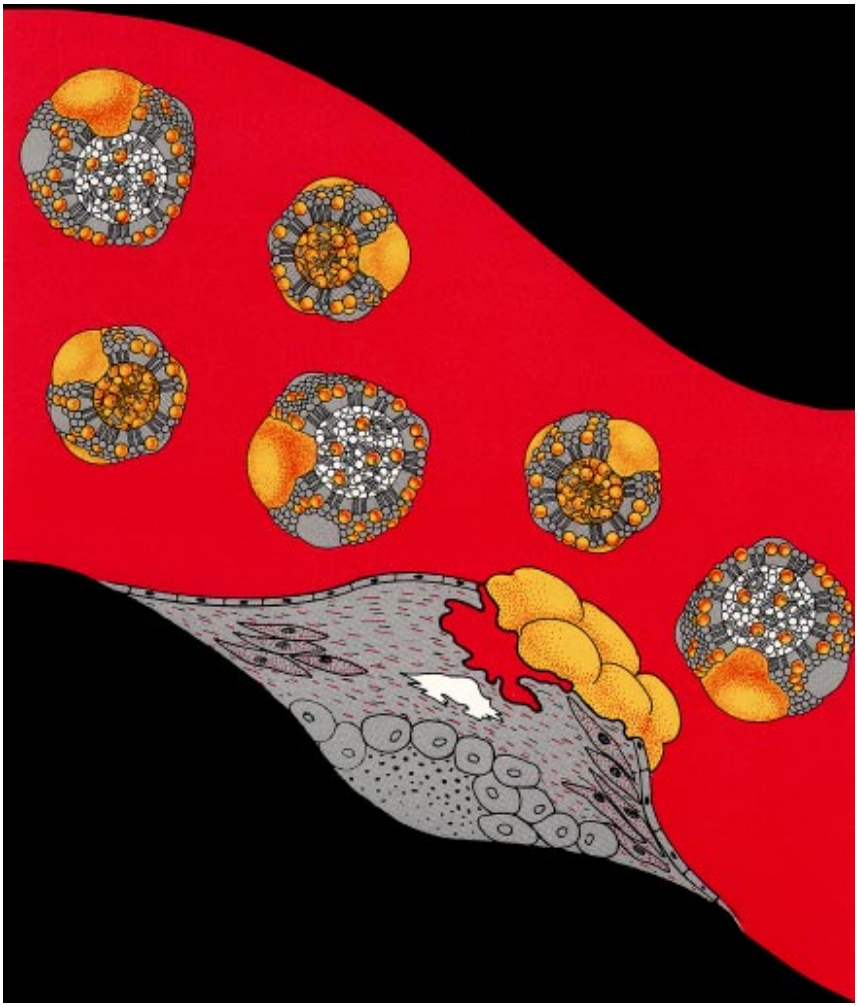

Triglyceride, High Density Lipoprotein, and Coronary Heart Disease

Consensus Statement

NIH Consensus Development Conference
February 26-28, 1992

Volume 10, Number 2

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For making bibliographic reference to the consensus statement from this conference, it is recommended that the following format be used, with or without source abbreviations, but without authorship attribution:

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This statement reflects the panel's assessment of medical knowledge available at the time the statement was written. Thus, it provides a "snapshot in time" of the state of knowledge on the conference topic. When reading the statement, keep in mind that new knowledge is inevitably accumulating through medical research.

Consensus Statement

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Abstract

The National Institutes of Health Consensus Development Conference on Triglyceride, High Density Lipoprotein, and Coronary Heart Disease brought together experts in lipid metabolism, epidemiologists, and clinicians as well as other health care professionals and the public to address the following questions: (1) Is the relationship of high triglcyeride and/or low HDL cholesterol with coronary heart disease causal? (2) Will reduction of high triglyceride and/or elevation of HDL cholesterol help prevent coronary heart disease? (3) Under what circumstances should triglycerides and HDL cholesterol be measured? (4) Under what circumstances should active intervention to lower triglyceride and/or raise HDL cholesterol be considered in high risk individuals and the general population? (5) What can be accomplished by dietary, other hygienic, and drug treatments? (6) What are the significant questions for future research? Following two days of presentations by experts and discussion by the audience, a consensus panel weighed the evidence and prepared their consensus statement.

Among their findings, the panel concluded that (1) existing data provide considerable support for a causal relationship between low HDL and CHD; however, with respect to TG data are mixed and the evidence on a causal relationship is incomplete; (2) initial TG and/or HDL levels modify benefit achieved by lowering low density lipoprotein cholesterol (LDL-C); however, evidence from clinical trials is insufficient to draw conclusions about specific benefits of TG and/or HDL altering therapy; (3) HDL-C measurement should be added to total cholesterol measurement when evaluating CHD risk in healthy individuals provided accuracy of measurement, appropriate counseling, and followup can be assured; (4) there is general agreement with the Adult Treatment Panel (ATP) guidelines that LDL-C is essential in cardiovascular risk assessment, as well as that persons with elevations of LDL-C greater than 150 mg/dl refractory to nondrug therapies may require drug treatment; (5) there is a strong consensus that hygienic approaches (diet, exercise, smoking cessation, weight loss) should be employed to lower TG and/or raise HDL; there is no consensus for the use of drug treatment in patients with borderline hypertriglyceridemia and low HDL-C levels in the presence of a desirable LDL-C level.

The full text of the consensus panel's statement follows.

Introduction

Great progress has been made over the past 30 years in identifying cardiovascular risk factors and in developing and implementing measures to correct them. The guidelines developed by the Adult Treatment Panel (ATP) of the National Cholesterol Education Program identified low density lipoprotein (LDL) as the major atherogenic lipoprotein and high levels of LDL cholesterol as the primary target for cholesterol-lowering therapy.

The ATP recognized low HDL cholesterol (< 35 mg/dl) as a major risk factor for coronary heart disease (CHD). It recommended that HDL cholesterol be measured in all patients with high blood cholesterol (≥240mg/dl) and in those patients with borderline high blood cholesterol (200-239 mg/dl) who had definite CHD or two other CHD risk factors (one of which could be male sex). Low HDL cholesterol was entered in the treatment decision algorithm as one of the major risk factors that would affect the assessment of overall coronary risk and therefore influence clinical decisions about treatment. The ATP report listed major causes of reduced serum HDL cholesterol, and although there had been no clinical trials demonstrating the benefit of raising HDL cholesterol, the ATP made recommendations to raise HDL concentrations by hygienic means. The report noted the possible benefit of raising HDL concomitant with reducing elevated LDL; however, drug therapy was not advocated specifically toraise HDL cholesterol in patients without high LDL cholesterol levels.

The ATP also addressed hypertriglyceridemia using definitions and recommendations of the National Institutes of Health Consensus Development Conference on Treatment of Hypertriglyceridemia, which convened in September 1983. The ATP regarded the relationship between plasma triglyceride levels and cardiovascular disease as controversial. The report stated that consistent evidence is lacking to support recognition of triglyceride as an independent risk factor of CHD. Instead, the ATP suggested that plasma triglyceride levels probably reflected the presence of certain atherogenic proteins and might be a clue to the presence of other lipoprotein abnormalities that were more directly associated with CHD, such as low HDL cholesterol, low apoprotein A-1, or elevated apoprotein B. It was noted that hypertriglyceridemia alone might be a marker for familial combined hyperlipidemia. The ATP further recognized that many disease entities that elevate triglyceride levels,

such as diabetes mellitus, nephrotic syndrome, and chronic renal disease, carry an increased risk of CHD. Other secondary causes of hypertriglyceridemia, such as commonly used drugs, also were listed. Hygienic measures were recommended for all individuals with hypertriglyceridemia; however, drug therapy was advocated only for those with marked hypertriglyceridemia who did not respond adequately to modification of diet. The ATP recommended that the triglyceride levels be measured in all patients with high blood cholesterol and in those patients with borderline high blood cholesterol who had definite CHD or two other CHD risk factors.

Since these guidelines were developed, the scientific data base has significantly expanded. Genetic investigations into familial dyslipidemias, advances in molecular biology, animal experiments, human observational studies, lipid metabolic studies, epidemiologic data, and the results of interventional clinical trials looking at mortality, cardiovascular endpoints, and angiographic changes in atheromatous lesions have created interest in further examination of the role of HDL cholesterol and triglycerides in the pathogenesis of coronary artery disease.

The consensus conference was designed to address the following questions:

- Is the relationship of high triglyceride and/or low HDL levels with coronary heart disease causal?
- Will reduction of high triglyceride and/or elevation of HDL cholesterol help prevent coronary heart disease?
- Under what circumstances should triglycerides and HDL be measured?
- What can be accomplished by dietary, drug, and other hygienic treatments?
- Under what circumstances should active intervention to lower triglyceride and/or raise HDL cholesterol be considered in high-risk individuals and the general population?
- What are the significant questions for continuing research?

To address these questions, the National Heart, Lung, and Blood Institute and the Office of Medical Applications of Research of the National Institutes of Health convened a Consensus Development Conference on Triglyceride, High Density Lipoprotein, and Coronary Heart Disease on February 26-28, 1992. After 2 days of presentations by experts and discussion by the audience, a consensus panel drawn from specialists and generalists from the medical profession and related scientific disciplines, clinical investigators, and public representatives considered the evidence and came to the following conclusions.

Is the Relationship of High Triglyceride and/or Low HDL Levels with Coronary Heart Disease Casual?

Associations between triglyceride, HDL, and coronary heart disease are well described in the literature. Causality may be inferred based on consistency of the data, strength of association, temporality, dose response, specificity, and biologic plausibility. The relevant observations for these criteria are described below.

HDL

A number of studies have been performed that have examined the relationship of HDL levels and the incidence of coronary heart disease. Studies of kindreds with familial forms of low HDL-C show that many affected members have CHD. Among 19 prospective epidemiologic studies, 15 have shown a significant and strong inverse relationship between HDL-C and CHD, 3 have shown an inverse trend, and one showed no trend. In the Framingham Heart Study, the Lipid Research Clinics (LRC) Mortality Followup Study, the LRC Coronary Primary Prevention Trial, and the Multiple Risk Factor Intervention Trial quantitative analysis of the data was consistent with a 2 to 3 percent decrease in CHD risk for each 1 mg/dl increase in HDL-C level, after adjustment to control for other risk factors. Followup extended from 6 to 10 years, and similar results were found in men and women. The limited information available on interventions which increase HDL-C suggests that this has a favorable effect on CHD. In studies of atherosclerosis regression, examination of coronary angiographic changes following interventions which increased HDL-C have generally shown positive results.

The concept that HDL may prevent the entry of cholesterol into the process of atherogenesis or even remove cholesterol from atherosclerotic lesions, so-called reverse cholesterol transport, has been supported by animal experiments. Two experiments suggest that affecting HDL may be beneficial. In one, HDL was infused into rabbits being fed atherogenic diets, and in the other, transgenic mice overexpressing human apoprotein A-1 were fed atherogenic diets. In both cases, there was less rapid progression of atherosclerosis.

However, there are still several unresolved issues. Unlike the situation with triglycerides, there is presently no information that examines HDL levels in relationship to alterations in coagulation factors. Not all individuals with inherited low HDL levels develop premature coronary heart disease. Subjects with genetic defects in the production of HDL have more CHD than those with defects in the catabolism of HDL. The reasons for these variations in CHD incidence are poorly understood, but further investigation of such cases may shed light on the role of HDL in atherogenesis. It is apparent, as in most lipoprotein fractions, that HDL is a heterogeneous collection of particles of differing size and composition and that subpopulations of HDL are altered in many of the dyslipidemias. It is not known to what extent these alterations of HDL contribute to atherogenesis and if all interventions affect these fractions in a similar way. The conclusions reached by the panel are related to studies reviewed based on American and European populations. These conclusions may not be necessarily applicable to populations with a low incidence of CHD.

Triglyceride

Observational studies using case control methods in patients with CHD have consistently shown a strong association of increased triglyceride with CHD. Most prospective cohort studies similarly show a strong positive relationship between triglyceride and CHD, demonstrating a dose response relationship. However, some studies suggest a specific level must be achieved for increased risk. When these same cohort studies are subjected to multivariate analysis, controlling for other risk factors such as blood pressure, physical activity, and obesity, the effect of triglyceride is diminished. The addition of indicators of abnormal glucose metabolism or HDL-C either eliminates or significantly reduces triglyceride as an independent predictor for risk.One possible explanation for the variability of these data may be found in the heterogeneity of the triglyceride containing lipoprotein and the biological variability of the measurement. The measurement of a single fasting triglyceride may inadequately represent this lipid. Individual triglyceride-rich lipoproteins, chylomicron remnants, intermediate density lipoproteins (IDL), very low density lipoproteins (VLDL), or particles of differing size and composition may be more closely related to CHD. Postprandial triglyceride may be more important than the fasting triglyceride levels, but little is known about this at the present time. In vitro studies find IDL, VLDL remnants, and other triglyceride-rich

lipoproteins to increase foam cell production. Some studies of atherosclerotic lesions have observed concentrations of triglyceride approximately twice those seen in the normal arterial wall. The triglyceride level of more advanced lesions does not rise as do the contents of cholesterol and cholesterol esters. This suggests that triglyceride may be metabolized within the arterial wall. Currently there is no animal model in which isolated elevations of triglyceride produce arterial lesions.

There are a number of genetic disorders with increased blood triglycerides. They may have either increased triglyceride synthesis or defects in removal. Many of these disorders (e.g., lipoprotein lipase deficiency and Apo-C-II deficiency) appear to have no increase in CHD despite elevated triglyceride levels. The VLDL and chylomicron particles of these patients are large and appear to lack atherogenic potential. However, other studies have reported premature CHD in hypertriglyceridemia, particularly when associated with hypertension or other lipid abnormalities characterized by small and apparently atherogenic VLDL and/or remnant particles as in familial combined hyperlipidemia and dysbetalipoproteinemia. In familial hypertriglyceridemia, some families have increased CHD, while others do not.

Recent data connect triglyceride levels with alterations of the coagulation system. Increased triglyceride levels are associated with increases in several coagulation factors (VII_c, $VIII_c$, and X_c) and altered fibrinolytic factors (increased PAI-1 and decreased tPA activity). Lowering of triglyceride by diet or drugs may normalize these clotting factors. It is suggested that some of the deleterious effects of elevated triglyceride on CHD may be mediated through its effects on the clotting and fibrinolytic mechanisms.

Clinical trials to specifically reduce triglyceride levels to prevent CHD have not been performed. Several trials in which the primary aim was to reduce LDL or total cholesterol have been done where triglyceride was measured. Four nonrandomized trials of lipid-lowering treatments measured triglyceride but failed to find any association with angiographic changes in coronary arteries. Of six randomized angiographic studies, five found no association despite triglyceride changes in all groups.

One study demonstrated changes in lesions associated with triglyceride, HDL-C, and LDL-C. Four large trials with CHD endpoints measured triglyceride, but three failed to show any association of triglyceride with CHD outcomes despite significant reductions in the intervention groups. The Stockholm Ischaemic Heart Disease Secondary Prevention Study did find an association with triglyceride reduction.

The inverse association of HDL-C with triglyceride is important in most circumstances. It is reasonable to infer that triglyceride plays an important role in the regulation of HDL metabolism. In this scenario, HDL would be the lipoprotein interactive with the plaque formation mechanisms, but triglyceride would play an important role in establishing the type, size, and quantity of HDL particles.

In prospective studies in which triglyceride has been considered jointly with HDL-C, LDL-C, total cholesterol, and other known CHD risk factors, multivariate statistical analyses generally have not shown triglyceride to be an independent risk factor for CHD. Because of a strong inverse correlation between triglyceride and HDL-C, relatively low precision of triglyceride measurements, and considerably higher variability of triglyceride values compared with cholesterol values, theoretical statistical analyses were recently performed. These analyses may underestimate the association between triglyceride and the risk of CHD.

There is limited evidence from a recent prospective observational study (PROCAM Study) suggesting that risk of CHD increased for individuals with relatively high LDL-C and low HDL-C with increasing triglycerides. In a recent primary prevention trial (Helsinki Heart Study), a subgroup analysis of individuals with high LDL-C and triglyceride and low HDL-C exhibited the largest benefit in reducing CHD. This subgroup analysis may be due to chance and warrants further study. There have been no intervention studies designed to address the question of the association of elevated triglyceride with CHD stratified by levels of HDL-C, LDL-C, and total cholesterol while controlling for other known CHD risk factors.

In summary, review of the information on HDL and CHD provides considerable support for a causal relationship. For triglyceride, the data are mixed; although strong associations are found in some studies, the evidence on a causal relation is still incomplete.

Will Reduction of High Triglyceride and/or Elevation of HDL Cholesterol Help Prevent Coronary Heart Disease?

The evidence most relevant to answer this question would consist of intervention trials with clinical or vascular imaging endpoints that demonstrated that reduction in very low density lipoproteins and/or elevations of HDL-C were associated with reduced clinical CHD events. These include fatal and nonfatal MI, angina, sudden death, need for coronary artery bypass graft surgery, angioplasty and other cardiovascular endpoints, or favorable changes in coronary lesions as evaluated by serial quantitative imaging of the coronary artery. Ideally, there would be quantitative correlations between the lipid-lipoprotein parameters and the study endpoints, and it would be shown that the lipoprotein alterations completely account for the favorable study endpoints. The data would be particularly convincing if total mortality also were favorably affected, and drug toxicity and drug side effects were acceptably low. Supporting data from appropriate experiments in animals would also be valuable.

Several large scale clinical trials involving both primary and secondary prevention have assessed the effects of lipid lowering on clinical coronary endpoints and have also measured total cholesterol, triglyceride, or HDL-C throughout the study. None of these trials was designed specifically to test the hypothesis that altering triglyceride or HDL-C concentrations would reduce coronary risk. Hence, none of the studies selected patients based solely on elevated triglyceride or low HDL-C. Instead, most studies sought to test the efficacy of lowering the LDL-C, and most subjects were chosen based on elevations of total cholesterol, LDL-C, or apolipoprotein B concentrations. Each of the interventions affected total cholesterol and/or LDL-C and one or more of the other components of the lipid profile. However, in only one of these studies, the Stockholm Ischaemic Heart Disease Secondary Prevention Study, was there a clear relationship between triglyceride levels in the treated group and beneficial change in CHD event rates. Since this study did not measure HDL levels, no conclusions could be drawn with regard to HDL. In the Lipid Research Clinics' Coronary Primary Prevention Trial, the overall decline

in CHD risk was 19 percent, 2 percent of which was attributable to an increase in HDL that was correlated with a 2 percent decline in CHD risk, and the benefit was greatest in those with a baseline HDL > 50 mg/dl. It should be noted that significant correlations were demonstrated also between lowering of LDL cholesterol and coronary risk. In the Helsinki Heart Study, a mean 12 percent rise in HDL-C and an 11 percent fall in LDL-C were both correlated with a 34 percent decline in CHD events. After correcting for HDL-C and LDL-C, no relationship between CHD events and triglyceride concentrations was found. Approximately 10 percent of the treated subjects had LDL-C/HDL-C ratios > 5 and triglyceride > 200 mg/dl. These patients had a 70 percent lowering of their CHD risk with gemfibrozil therapy, suggesting that a subgroup at especially high risk and particularly sensitive to therapy had been identified. The relative lowering of risk in other subgroups was considerably less.

In a review of trials using angiographic endpoints employing randomization, interventions designed to alter lipoprotein levels caused small but generally favorable changes in coronary arteries (decreased progression, stabilization of lesions and possible regression in some cases, and less new lesion formation). These angiographic changes were associated with favorable outcome. However, attempts to correlate the favorable vascular changes to either total triglyceride reduction or HDL-C elevation have yielded no consistent trends.

Although the evidence from clinical trials is insufficient to draw conclusions about the specific benefits of perturbing triglyceride and/or HDL levels, lipid-lowering therapy is an effective strategy in CHD prevention. In most studies, the benefits are correlated with changes in LDL-C, but initial triglyceride and/or HDL concentrations play important modifying roles in determining the degree of benefits achieved. These modifying roles suggest that atherogenic and anti-atherogenic subfractions may be present in VLDL and HDL fractions, respectively. At the present time these fractions are not being specifically measured when determinations of triglyceride and HDL-C concentrations are normally carried out, as is noted in our response to question 1.

Under What Circumstances Should Triglyceride and HDL Be Measured?

Risk assessment using total cholesterol levels has proven valuable in identifying patients who are at elevated risk for atherosclerotic cardiovascular diseases. However, epidemiological data have demonstrated that a substantial percentage of patients who develop CHD have total cholesterol levels in the desirable range. Accordingly, HDL-cholesterol and triglyceride measurements have been proposed as additional methods to improve risk assessments.

The panel recommends assay of HDL-C levels under the following circumstance: HDL-C measurement should be added to total cholesterol measurement when evaluating CHD risk in healthy individuals provided accuracy of measurement, appropriate counseling, and followup can be assured.

The panel recommends assay of both HDL and triglyceride levels under the following circumstances:

- To assess risks for progression of disease and development of additional cardiovascular complications in persons with known CHD.

- To refine CHD risk assessment in those with increased total cholesterol (above the desirable range). Here, HDL-C and triglycerides should be measured to identify those who may have high HDL-C and desirable LDL-C and, therefore, be at low to average risk for CHD.

- To refine CHD risk assessment in those with desirable total cholesterol who have 2 or more CHD risk factors (e.g., male sex, postmenopausal female, hypertension, family history, smoking, diabetes). In this setting, HDL-C and triglyceride should be measured to identify those who may have low HDL-C and/or high triglyceride and, therefore, actually be at additional risk for CHD.

- To refine CHD risk assessment in patients with other disorders which may be associated with increased triglyceride and are known to be associated with increased CHD risk (e.g., diabetes, peripheral vascular disease, hypertension, central obesity, chronic renal disease).

- In patients with lactescent serum, lipemia retinalis, xanthomata, or pancreatitis, to determine the presence of familial hyperlipidemic disorders and/or the likelihood for recurrence of pancreatitis and to follow triglyceride response to treatment in such cases when triglyceride is elevated, triglyceride should be measured.

- To follow results of nonpharmacologic and/or pharmacologic therapy directed toward reductions of triglyceride and/or increases of HDL-C in order to assess treatment effect.

Measurement Considerations

The extent to which HDL-C and triglyceride levels can be used to assess risk for CHD depends, among other things, on the accuracy and reliability with which these plasma lipids can be measured. Imprecision in these measurements relates to both biologic and analytical variations. The biologic variation for HDL-C measurements, expressed as coefficient of variation (CV), is approximately 7 to 8 percent, and the analytical variation is approximately 6 percent (CV). For triglyceride, the biologic variation approximates 20 percent (CV) and analytical variation, 5 percent (CV). In addition, the variability is dependent upon prior alcohol intake, posture, concomitant medications and hormones, prior exercise status, diet, menstrual cycle, time of day (a.m.), and sample collection (e.g., concentration of anticoagulant in the blood filled tube and storage). Standardizing these factors will reduce the variability. Accordingly, using current techniques for HDL and triglyceride analysis, at least two, ideally three, samples, taken in the fasting state at least 1 week apart, are generally recommended in order to enhance precision before treatment decisions are finalized.

What Can Be Accomplished By Dietary, Drug, and Other Hygienic Treatments?

Lifestyle factors that significantly aggravate hypertriglyceridemia and low HDL-C levels are obesity, smoking, and sedentary lifestyle. Thus, diet and weight control, exercise, and smoking cessation must be the emphasis of treatment for elevated triglyceride and low HDL-C levels. Treatment should be individualized and targeted to the causative factor(s).

A National Cholesterol Education Program/American Heart Association Step-One diet is recommended for all patients with elevated triglycerides. Some patients will require a Step-Two diet to achieve further modifications in plasma lipids. A Step-One diet provides 30 percent of calories from fat, less than 10 percent of calories from saturated fatty acids, up to 10 percent of calories from polyunsaturated fatty acids, up to 15 percent of calories from monounsaturated fatty acids, and < 300 mg of cholesterol. A Step-Two diet provides < 7 percent of calories from saturated fatty acids, and < 200 mg of cholesterol. These diets are effective in achieving a plasma total and LDL-C lowering, facilitate achieving and maintaining a healthy weight, and aid in managing elevated triglycerides.

Obesity/Overweight and Excess Calories

Obesity/overweight and excess calories frequently are associated with hypertriglyceridemia and low HDL-C levels. Frequently, weight loss alone can significantly decrease plasma triglycerides and increase HDL-C levels. Achieving and maintaining a healthy weight by diet (calorie control) and regular exercise are important in managing elevated triglyceride and low HDL-C levels. Frequently, weight loss alone normalizes plasma triglycerides; combined with a program of regular exercise, HDL-C levels may increase 10 to 20 percent.

Alcohol

Alcohol increases plasma triglycerides in some patients and increases HDL-C. In patients with very high triglycerides, alcohol should be eliminated. Because of inherent problems, as well as its effects on triglycerides, alcohol use to raise HDL-C is not recommended.

Carbohydrate

A high carbohydrate diet has been shown to increase plasma triglycerides and decrease HDL-C levels. These diets lead to the production of large buoyant VLDL particles, which are thought to be less atherogenic compared to dense VLDL particles. In societies that have a high carbohydrate diet and a low incidence of CHD, plasma triglycerides are slightly higher and both LDL-C and HDL-C are lower than in societies that consume a Western diet. Thus, low HDL-C levels of themselves may not be deleterious under these circumstances. The Step-One and Step-Two diets should emphasize complex carbohydrates and fiber for the treatment of elevated triglycerides. Some patients may initially experience a slight increase in plasma triglycerides on a Step-One and Step-Two diet; however, these patients should have more favorable lipid/lipoprotein profiles (i.e., lower plasma total cholesterol and LDL-C levels) and therefore a lower risk of CHD.

Fish and Fish Oil

From population studies, diets high in fish are associated with reduced CHD risk. Fish oils and omega-3 fatty acids result in decreased triglycerides, and may increase LDL-C and/or apolipoprotein B level(s). They also impair clotting and diabetic control. Omega-3 fatty acids, in large amounts, may reduce excessive triglyceride levels that do not respond adequately to recommended dietary therapy.

Exercise

Exercise increases HDL-C and decreases plasma triglycerides and the risk of CHD. Intervention studies have shown that there is a dose-response relationship between HDL-C levels and the amount (frequency, intensity, duration) of exercise. In general, intervention studies report a 10 to 20 percent increase in HDL-C in response to an exercise program. The decrease in HDL-C in response to a diet that is lower in total fat, saturated fat, and cholesterol can be prevented/attenuated by a regular exercise program. A program of regular exercise is important in achieving and maintaining a healthy weight.

Cigarette Smoking

Cigarette smoking decreases HDL-C and is a powerful risk factor for coronary heart disease. A recent study suggests that passive smoking also decreases HDL-C. Smoking cessation increases HDL-C and reduces CHD risk.

Summary of Hygienic Therapy

The primary therapy for the treatment of elevated triglyceride and low HDL-C levels is diet and weight control, exercise, and smoking cessation. Hygienic measures always should be used first, and rigorous intervention is recommended. For many patients, triglycerides and HDL-C can be normalized by these interventions alone.

Patients are likely to benefit from the services of health professionals such as registered dieticians and other qualified nutritionists, exercise physiologists, and health educators. Third-party reimbursement for these services is recommended to decrease the significant barriers that exist in enabling patients to realize the full benefits of hygienic therapy.

Pharmacologic Therapy

Pharmacologic therapy of hypertriglyceridemia and low HDL is relegated to a secondary role for the reasons indicated above. All medications have side effects, and potential risks must be balanced with potential for benefit before their use can be justified.

Oral estrogens alter plasma lipoproteins and, from extensive observational studies in postmenopausal women, appear to reduce coronary heart disease by approximately 50 percent. In usual clinical doses, they lower LDL-C and increase HDL and triglycerides. Information is lacking on the effect of estrogen-induced changes in HDL subfractions, apolipoproteins, or the risks of CHD when triglyceride levels are increased. There is a risk of increased incidence of endometrial cancer and possible increase in the risk of breast cancer. Although extensive observational data indicate that there is benefit of estrogens in CHD, the most common cause of death in postmenopausal women, evidence from randomized prospective clinical trials demonstrating benefit in coronary heart disease is lacking.

Nicotinic acid decreases triglycerides in proportion to their elevation and is very effective in increasing low HDL. There is a relative contraindication for use in patients with noninsulin-dependent diabetes. Niacin is a first choice when drugs are required because of its low cost and its efficacy in altering multiple lipid fractions. The combination of diet, bile acid sequestrants, and niacin reduced progression of atherosclerosis and appearance of new lesions in patients with and without coronary bypass grafts.

Fibric acid derivatives decrease triglycerides and increased HDL-C. One fibric acid derivative, gemfibrozil, has been associated with reduced risk of CHD in patients with mixed hyperlipidemia and low HDL levels.

Bile acid sequestrants induce a small increment in triglycerides and in HDL. Their use is not recommended in patients with significant hypertriglyceridemia.

HMGCoA reductase inhibitors decrease triglycerides in the intermediate levels and increase HDL in patients with hypercholesterolemia and low HDL. They have modest effectiveness on higher triglyceride levels.

Under What Circumstances Should Active Intervention to Lower Triglyceride and/or Raise HDL Cholesterol Be Considered in High-Risk Individuals and the General Population?

Rationale

The rationale for treatment of hypertriglyceridemia is based on observational studies in which triglyceride levels correlated directly with coronary heart disease. In addition, certain genetic forms of hyperlipidemia—such as familial combined hyperlipidemia, familial type 3 hyperlipidemia, and some families with familial hypertriglyceridemia—are associated with an increased incidence of CHD. In these disorders, VLDL or its remnants or remnants of chylomicrons accumulate in plasma and are thought to result in atheroma formation. Hypertriglyceridemia is also frequently associated with other abnormalities which may predispose to atherosclerosis. These include low HDL-C levels, an increased number of small dense LDL particles, an increased concentration of postprandial lipoproteins, and altered levels of coagulation factors that may either favor thrombosis or inhibit fibrinolysis. Furthermore, patients with very high triglyceride levels (generally exceeding 1000 mg/dl) are prone to develop pancreatitis.

The rationale for treating low HDL-C is also based on observational data relating cardiovascular risk inversely to HDL-C levels. In addition, results of several intervention trials indicate that the benefit of treatment was partially related to an increase in HDL-C. The hygienic measures and drugs that reduce triglycerides and/or raise HDL-C were discussed in the previous section.

Definition of High Triglyceride or Low HDL-C for Cardiovascular Disease Risk

The previous consensus development panel on hypertriglyceridemia classified triglyceride levels into distinct hypertriglyceridemia (triglyceride level > 500 mg/dl) and borderline hypertriglyceridemia (triglyceride level 250 to 500 mg/dl). The current consensus panel found no clear evidence to indicate a need for change in this classification. With regard to HDL-C, a range of levels correlates inversely with CHD risk, and the panel arbitrarily selected < 35 mg/dl as the cut-point for identifying individuals with very high risk. This level may be too low in women and possibly other specific subpopulations, but it

conforms with existing National Cholesterol Education Program (NCEP) guidelines. No compelling data were identified that would currently dictate a change in the use of this HDL-C cut-point.

Use of Triglyceride and HDL-C in the Assessment of Patients

The metabolism of the lipoprotein classes in plasma is interrelated, and patients frequently display abnormalities in more than one lipoprotein. Therefore, the triglyceride and HDL-C levels cannot be interpreted in the absence of the LDL-C level. Since the LDL-C is essential in cardiovascular risk assessment, a reasonable approach to the evaluation of HDL-C and triglyceride levels in patients is to include the LDL-C level in making therapeutic decisions as recommended by the ATP of the NCEP.

There is general agreement with the NCEP guidelines to the effect that persons with elevations of LDL-C greater than 160 mg/dL refractory to nondrug therapies may require drug treatment. The other factors entering into a decision to use drugs include the presence of CHD or other CHD risk factors such as low HDL-C, family history for CHD, diabetes mellitus, hypertension, cigarette smoking, male gender, and obesity. Accumulating evidence suggests that the postmenopausal state in women should also be considered a CHD risk factor. Current data from the Helsinki Heart Study and the PROCAM Study indicate that elevated triglyceride concentrations may also contribute to risk assessment and hence should be considered in making therapeutic decisions. In the absence of any of these risk factors, CHD, or in the presence of a very high HDL-C level, drug therapy is not indicated for borderline high risk LDL-C levels (130-160 mg/dl).

There is no consensus for the use of drug treatment in patients with borderline hypertriglyceridemia and low HDL-C levels in the presence of a desirable LDL-C level. There is strong consensus that hygienic approaches (diet, exercise, smoking cessation, weight loss) should be employed. Drug treatment should be considered in cases where hygienic approaches fail, and CHD or a strong coronary risk profileis present. No intervention trials to test this approach (lowering triglyceride and/or raising HDL-C with drugs) have been reported in this type of patient.

Distinct hypertriglyceridemia (500 mg/dl and above) should be managed initially with hygienic measures. If hypertriglyceridemia persists, drug therapy is warranted to reduce the

risk for pancreatitis. When a history of pancreatitis is already present, drug treatment should be considered as the initial therapy in conjunction with the hygienic measures. Patients who fail to respond to drug therapy may have lipoprotein lipase deficiency or apolipoprotein C-II deficiency and require expert evaluation.

Very low or absent HDL-C levels in patients with desirable LDL-C and high triglyceride levels probably represent rare genetic disorders that require expert evaluation. Often these patients have genetic mutations affecting one or more of the apolipoproteins in HDL particles. There is no specific therapy at this time for these patients.

Primary hypoalphalipoproteinemia is a relatively uncommon familial disorder with low HDL-C levels and generally normal LDL-C and triglyceride levels. These patients appear to be at increased risk for CHD. Therapy should include hygienic measures and control of coexisting CHD risk factors. Drugs that ordinarily raise HDL-C may be ineffective in these patients. Therefore, some experts have taken the approach that therapy should be directed toward lowering the LDL-C concentrations. However, it must be noted that no intervention trials have been performed to test the validity of this approach.

Beyond the clinical situations enumerated above, there is no consensus for treating mild non-familial hypertriglyceridemia and/or low HDL-C levels with drugs in the absence of other major risk factors.

What Are the Significant Questions for Continuing Research?

- We encourage the development of precise, accurate, rapid, and inexpensive measurements of plasma lipid concentrations and other atherogenic particles.
- More research is needed to identify and quantify atherogenic and antiatherogenic subfractions which may be present in VLDL and HDL.
- Additional studies are needed to determine the interrelationships of altered lipid metabolism and thrombosis in atherogenesis.
- Additional studies are desirable to provide information on the atherogenic effects of high triglycerides and low HDL in animal models. Development of appropriate animal models is encouraged.
- Primary and secondary prevention trials need to examine the benefits of decreasing triglyceride and raising HDL-C in patients selected on the basis of high triglyceride and/or low HDL levels.
- Studies should be initiated to determine the association of CHD with cholesterol and lipoprotein fractions in minority populations.
- Additional studies are needed to assess the impact of lifestyle modification on the elevation of low HDL-C. The effects of estrogen and progesterone use on HDL subfractions, apolipoproteins, Lp(a), and the effects of these lipids on CHD risk in women is needed.
- We recommend the development of methods to make hygienic intervention more effective to larger segments of our society, including those with low literacy skills.
- We wish to foster the development of methods, preferably noninvasive, to image the vascular wall in order to characterize plaque composition and quantify its size and distribution.
- Further studies are needed to evaluate the effects of diet on plasma lipoproteins, their composition, production and clearance, and measures of hemostasis.

Conclusions

Considerable evidence is available suggesting that a causal association exists between the presence of a low plasma HDL cholesterol and the subsequent development of coronary heart disease. Current evidence does not allow one to conclude that comparable causality exists between the presence of high levels of plasma triglyceride and coronary heart disease. Nevertheless, triglyceride-rich lipoproteins can be atherogenic. Furthermore, elevated triglycerides produce increases in several clotting factors and decrease fibrinolytic activity which may contribute over time to the atherosclerotic process.

Triglyceride levels correlate in many prospective studies with coronary events. However, when multivariate statistical analyses are carried out that adjust for HDL-C, LDL-C, and total cholesterol and other risk factors, this correlation is frequently lost. There is some limited evidence, nevertheless, that suggests that the risk of CHD increases as triglyceride increases in patients exhibiting high levels of total or LDL cholesterol and low levels of HDL-cholesterol.

Evidence from existing clinical trials is inadequate to conclude that lowering triglyceride will decrease the risk of CHD. Reduction in CHD frequently occurs when patients with elevated LDL cholesterol are treated with hygienic measures and/or drugs. It seems desirable based on secondary prevention trials and angiographic studies of coronary atherosclerosis to treat CHD patients with low HDL and elevated triglyceride levels even in the presence of a desirable total cholesterol. Such treatment should begin with hygienic measures but drug use may be entertained if these measures prove ineffective.

The panel recommends that HDL determinations should accompany measurements of total cholesterol when healthy individuals are being assessed for CHD risk. The panel cautions, however, that this be done in locations where accuracy of measurement, appropriate counseling, and followup can be assured. This is particularly important because of the increased biologic and analytical variation inherent in its measurement. The panel also recommends that HDL-C and triglyceride levels be determined in healthy individuals with high total cholesterol and in those who have two or more of the known CHD risk factors.

Patients with diabetes, central obesity, peripheral vascular disease, hypertension, and chronic renal disease, which are known to be associated with an increased risk of CHD, should have triglyceride levels measured. Triglycerides should also be measured where familial hyperlipidemic disorders are suspected and to follow the results of therapy when patients are treated for elevated triglycerides. Finally, HDL-C and triglycerides should accompany measurements of total cholesterol in patients with known CHD.

Hygienic measures should always be employed when triglycerides are elevated or HDL cholesterol is low regardless of total cholesterol. Drugs, however, should be used sparingly under these circumstances in the absence of an elevation of LDL cholesterol in individuals without known CHD.

It is clear that many important questions remain unanswered regarding the impact of these two major lipid fractions.

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"Is HDL a Risk Factor?"

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"Is Triglyceride a Risk Factor?"

Gerd Assmann, M.D.
"The PROCAM Study"

Gerardo Heiss, M.D., Ph.D.
"The LRC Followup Study"

Trudy L. Bush, Ph.D., M.H.S.
"Estrogens, HDL, and Coronary Heart Disease in Women"

Rodolfo Paoletti, M.D.
"Discussion"

Lawrence L. Rudel, Ph.D.
"Human and Animal Pathology: Evidence From Animal Experiments (The Relationship of Triglycerides and HDL in Blood to Experimental Coronary Artery Atherosclerosis)"

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"Structure and Metabolism"

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"Anti-Atherogenicity of HDL"

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"Atherogenicity of Triglyceride"

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"HDL, Triglyceride, and the Coagulation System"

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"HDL Syndromes and Coronary Heart Disease"

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"High Triglyceride Syndromes"

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"Trials of Clinical Endpoints"

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"Angiographic Studies"

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"Helsinki Heart Study"

Paul S. Bachorik, Ph.D.
"Measurement of HDL and Triglyceride"

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"The Case For or Against Population Screening (Population Screening for High Triglyceride and Low HDL-Cholesterol)"

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"The Case For or Against Population Screening"

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"Secondary Causes of Low HDL and High Triglyceride and Their Management"

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"Efficacy of Diet and Drug Therapy"

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"Hygienic Interventions"

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"Approach to Management of Low HDL and High Triglycerides" (Managing Hypertriglyceridemia and Low Levels of High Density Lipoprotein Cholesterol: Recommendations of the International Committee)"

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