INTRODUCTION

According to the American Heart Association [2004], coronary heart disease (CHD) is the leading cause of death in the United States today. Also referred to as coronary artery disease (CAD), CHD is caused by atherosclerosis, which is defined as the narrowing of the blood vessels supplying the heart (coronary arteries) due to accumulation of fatty substances, cholesterol, cellular waste products, calcium, and fibrin, resulting in the formation of plaques. Research has indicated that elevated low-density lipoprotein cholesterol (LDL-C) is a major cause of CHD, and recent clinical trials have shown that LDL-C lowering therapy reduces risk for CHD [Scandinavian Simvastatin Survival Study Group, 1994; Downs et al., 1998; Heart Protection Study Collaborative Group, 2002].

In 2001, the National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP III) suggested the first line of therapy for improving cardiac health should include dietary and behavioral changes, otherwise defined as therapeutic lifestyle changes (TLC). While ATP III recommends more intensive LDL-C lowering therapy for certain high-risk groups, the core principles are based on the guidelines established in ATP I and II. The initial guideline report (ATP I) defined CHD prevention strategies in patients with high levels of LDL-C ($\geq$160 mg/dL), or borderline high LDL-C (range 130-159 mg/dL). The second guideline report (ATP II) established a lower LDL-C goal for persons with established CHD ($\leq$100 mg/dL).

In order to favorably alter serum lipid levels, ATP III's clinical approach to primary prevention calls for (1) reduced intakes of saturated fat and cholesterol, (2) increased physical activity, and (3) weight control. Due to current research suggesting LDL-C is directly correlated with CHD risk, ATP III continues to identify elevated LDL-C as the primary target of cholesterol-lowering therapy.

TREATMENT OPTIONS

Currently there exist many treatment options for individuals with hypercholesteremia, defined as total serum cholesterol concentrations $\geq$240 mg/dL. These strategies include dietary changes, increased physical activity, and pharmacotherapeutics.

DIETARY MODIFICATIONS

Current research suggests that reductions in intake of foods rich in saturated fats and cholesterol can lower LDL-C levels by approximately 5% to 10% [Cleement and Lenfant, 1998]. Therefore, reductions in the intake of high-cholesterol foods, such as red meats, whole milks, cheeses, etc, can have limitations on cholesterol lowering abilities. The addition of plant sterols, vegetable proteins, and viscous fiber containing foods into daily diet, however, may provide favorable therapeutic results [Jenkins et al., 2002]. Given the structural similarity of plant sterols and stanols to cholesterol [Law, 2000; Ostlund, 2004], they appear to inhibit the uptake of dietary and biliary cholesterol in the distal small intestine by competing with cholesterol for incorporation into mixed micelles (particles involved in lipid and cholesterol transport across the intestinal epithelia). By competitively inhibiting enteric absorption of cholesterol, there is increased fecal cholesterol loss, which results in favorable reductions of serum LDL-C and other cholesterol subfractions [Ling and Jones, 1995].

PHARMACOTHERAPY

Statins, or 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, competitively inhibit hepatic cholesterol metabolism. This results in increased hepatic LDL-receptor expression and a subsequent increase in cholesterol uptake. Statins have repeatedly been shown to reduce mean serum LDL-C concentrations by 28% to 35% in long-term trials [Scandinavian Simvastatin Survival Study Group, 1994; Downs et al., 1998; Heart Protection Study Collaborative Group, 2002]. More recent studies have suggested favorable outcomes for hyperlipidemic, diabetic patients [Collins, 2003].

Bile sequestering agents are non-absorbable resins which prevent the reuptake of bile acids in the distal ilium, resulting in decreased cholesterol absorption. Unfortunately, compliance among patients is extremely low, and many are unable to tolerate the oral administration of such resin products. In terms of pharmacotherapies, statins have overtaken bile sequestering agents as the drug of choice for cholesterol lowering medications.

HDL Therapies

In contrast to LDL-C, high-density lipoprotein cholesterol (HDL-C) levels are inversely proportional to CHD risk [Park and Ransone, 2003]. Physical exercise, weight reduction, smoking cessation, diabetes mellitus control, and specific drugs, including niacin, fibrates, and estrogens, are effective methods to increase HDL-C levels [Kashyap, 1998]. Based on in vitro experiments, several mechanistic explanations for the atheroprotective function of HDL-C have been suggested. While many of these mechanisms have yet to be elucidated in relevant models, the most widely accepted explanations for the antiatherogenic effect include participation in reverse cholesterol transport, protection against endothelial dysfunction, and inhibition of oxidative stress [Assmann and Nofer, 2003].

Recent Studies

Dietary Portfolio

Despite the rationale of utilizing dietary manipulations for modest cholesterol reductions of 5% to 10%, diet has been considered by some as a relatively ineffective therapy [Ramsay et al., 1991]. Whether or not the combined effects of plant sterols, vegetable proteins, and viscous fibers would result in an addition, synergy, or quenching of their individual cholesterol-lowering effects had not been studied previously. Following an initial study based on dietary portfolios in thirteen patients [Jenkins et al., 2002], Jenkins and colleagues went on to compare dietary portfolio to statin therapy. In a randomized parallel design study [Jenkins et al., 2003], a group of hyperlipidemic adults were randomized to 1 of 3 treatments: the combination dietary portfolio, a diet lacking the additional active dietary ingredients but with similar very low-saturated-fat content (control), or the same low-saturated-fat diet with addition of lovastatin, a first-generation statin marketed for cholesterol reduction. At the conclusion of the 4-week study, forty-six healthy, hyperlipidemic participants completed their respective treatments (25 men and 21 postmenopausal women), with 7 participants lost for reasons unrelated to the study, and 2 who were withdrawn due to elevated liver enzymes or symptoms of muscle discomfort (intention-to-treat analysis was performed). The mean age was 59 years (range, 36-85 years) and mean body mass index was 27.6 (range, 20.5-33.5). All participants had previously determined elevated LDL-C levels (>158 mg/dL), although none of the participants had a history of cardiovascular disease, untreated hypertension (blood pressure >140/90 mm Hg), diabetes, or renal or liver disease, and none were taking medications known to exert affects on serum lipids apart from 3 women who were taking stable doses of thyroxine, 1 of whom was also taking estrogen therapy. In the statin and dietary portfolio groups, the results included statistically significant reductions in LDL-C levels (-30.9% and -28.6%, respectively), LDL-C-HDL-C ratios (-28.4% and -23.5%, respectively), and C-reactive protein (-33.3% and -28.2%, respectively). Calculated coronary heart disease (CHD) risk was reduced in similar fashion (-25.8% and -24.9%, respectively). While all differences were statistically significant in comparison to control, no significant differences were noted between the dietary portfolio and statin groups. No significant treatment differences were observed in blood pressure.

Exercise, Sterols, and Combination Therapy

Previously, no study had tested the effect of an 8-week moderate intensity exercise program on lipid and lipoprotein response. Furthermore, no study had observed the combined complementary effects of plant sterols and endurance training on plasma lipid and lipoprotein cholesterol, as well as sterol and cholesterol precursor concentrations in previously sedentary hypercholesteremic adults at risk for coronary artery disease (CAD). In an 8-week, placebo-controlled, single-blind, parallel-arm clinical trial [Varady et al., 2004], 84 subjects were randomly assigned to receive 1 of 4 interventions: 1) combination of sterol and exercise, 2) exercise, 3) sterols, or 4) control treatment. 74 participants completed the study, with results for combination, exercise, and sterol groups as follows: total cholesterol reductions (-5.4%, 2.1%, and -7.1%, respectively), LDL-C changes (-5.9%, 6.9%, and -11.3%, respectively), HDL-C increases (9.2%, 11.2%, and 5.8%, respectively), and triacylglycerol concentration reductions (-9.7%, -14.5%, and -1.3%, respectively). In terms of plasma cholesterol precursor and plant sterol alterations, the results were as follows: lathosterol increases (20.2%, 3.2%, and 14.8%, respectively), campesterol alterations (44.2%, -0.3%, and 49.1%, respectively), and β-sitosterol increases (20.1%, 3.9%, and 27.0%, respectively). Finally, the results for changes in body weight in the combination and exercise groups were -1.4% and -1.2, respectively. Changes in percentage body fat in the combination and exercise groups were -4.2% and -3.1%, respectively.

REVERSAL TRIAL

Recent studies have suggested portfolio diets and low-dose statin regimens provide therapeutic benefits in terms of lowering LDL-C as well as triacyglycerols. However, the prevention of coronary artery atheroma, which is the ultimate goal of the portfolio diet and statin regimens, has yet to be examined directly. In order to examine the direct effects of intensive and moderate lipid lowering statin regimens, a double-blind, randomized active control multi-center trial (Reversal of Atherosclerosis with Aggressive Lipid Lowering [REVERSAL]) performed at 34 community and tertiary care centers in the United States comparing the effects of 2 different statins over the course of 18 months was carried out [Nissen et al., 2004]. Participants were randomized to receive either a moderate lipid-lowering medication of 40 mg pravastatin (Pravachol) or an intensive lipid-lowering medication of 80 mg atorvastatin (Lipitor). Intravascular ultrasound was used to measure the progression of atherosclerosis. In between June 1999 and September 2001, a total of 654 patients were randomized and received the study drug, with 502 having observable intravascular ultrasound examinations at baseline and after 18 months of treatment. Mean baseline LDL-C levels of 150.2 mg/dL were reduced to 110 mg/dL in the pravastatin group and to 70 mg/dL in the atorvastatin group. C-reactive protein decreased approximately 5.2% and 36.4% in the pravastatin and atorvastatin groups, respectively. More importantly, percentage change in atheroma volume showed a significantly lower progression rate in the atorvastatin group, whereas progression of coronary atherosclerosis occurred in the pravastatin group.

DISCUSSION

As provided by the NCEP ATP III, there is adequate evidence-based medicine to provide all fields of medicine with effective methods for achieving favorable serum lipid levels. Whether solely utilizing dietary portfolios, or in conjunction with exercise and/or pharmacotherapy, the studies described above offer valuable guidelines for primary and secondary prevention of CHD. As would be expected, dietary changes, such as the dietary portfolio, may be especially relevant in persons with lipid concentrations or risk factors just below the cut-off point for drug therapy. Furthermore, therapeutic lifestyle changes may be the only option for those persons in which drug-therapies are contraindicated.

Jenkins et al. [2003] illustrated equal effectiveness in cholesterol-lowering when comparing statin and dietary portfolio treatments. Varady et al. [2004] suggest that the combination of plant sterols and endurance training results in greater lipid-altering effects when compared to that of each intervention alone. Furthermore, their study was the first to demonstrate improvements in HDL-C and triacylglycerol concentrations from short-term (8-week) endurance training. While efficacies may have proven effective, the duration of these studies may call into question the likelihood patients may be able to sustain such regimens over extended periods of time. Follow-up studies should examine relapse rates into old dietary habits and sedentary lifestyles with subsequent serum lipid analysis. Additionally, the relevance of endurance training falls short in certain patient populations. For those of lower socio-economic status, cost and safety are likely to pose as obstacles in obtaining foods and locations for endurance training, respectively. Despite these criticisms, the evidence from both studies provide further support for the guidelines established by the NCEP ATP III, which strongly recommends therapeutic lifestyle changes (TLC) as first-line therapy for primary prevention of CHD.

In perhaps the most striking study of all, Nissen et al. [2004] demonstrated that in patients with established CHD, intensive lipid-lowering treatment with atorvastatin reduced progression of coronary atherosclerosis compared with pravastatin. Compared to baseline values, patients treated with atorvastatin had no change in atheroma burden, whereas patients treated with pravastatin (moderate therapy) exhibited progression of coronary atherosclerosis. In contrast to the studies discussed earlier, which allude to non-pharmacotherapeutics for primary prevention, pharmacotherapy appears to be required for secondary prevention. Based on research and conclusions made from this study, it would seem unlikely that dietary portfolios and endurance training, alone, would be sufficient to halt or slow the progression of coronary atherosclerosis. However, studies have yet to be conducted comparing the effects of such lifestyle changes, either as single modalities of secondary prevention, or in conjunction with current available medications. In terms of primary prevention of CHD and for elevated cholesterol management, dietary changes appear to be the most reasonable approach. As indicated by ATP III, however, certain patient groups may require additional therapy, and the most effective methods for secondary prevention have yet to be fully elucidated.

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