Familial Type II Hyperlipoproteinemia with Coronary Heart Disease*

Effect of Diet-Colestipol-Nicotinic Acid Treatment

Peter T. Kuo, M.D., F.C.C.P.; John B. Kostis, M.D., F.C.C.P.;
A.E. Moreyra, M.D.; and J.A. Hayes, M.D.

Heterozygous familial type II hyperlipoproteinemia (F type II) is primarily manifested in hypercholesterolemia (due to low density lipoprotein-cholesterol [LDL-C] elevation) and premature coronary heart disease (CHD). We studied sequentially the effects of low cholesterol-low saturated fat-low simple carbohydrate diet; diet and colestipol, 30 g/day; and diet, colestipol, plus nicotinic acid (NA) 3 to 7 g/day on plasma cholesterol (Ch), LDL-C, triglyceride (TG), high density lipoprotein-cholesterol (HDL-C) and angiographically documented coronary arterial lesions of 32 F type II patients. Effective control of F type II resulted in arresting the progression of angiographically demonstrated coronary arterial lesions.

Familial type II hyperlipoproteinemia (F type II) is a hereditary disorder characterized by hypercholesterolemia due to high levels of low density lipoprotein (LDL), and by early development of atherosclerosis frequently manifested in premature coronary artery disease (CAD). Recent studies made on human and nonhuman primates suggest that a substantial reduction in plasma cholesterol, especially in low density lipoprotein cholesterol (LDL-C), is required to promote either stabilization or regression of atherosclerosis, and a potent combination of diet and drugs is required to accomplish the desirable degrees of plasma cholesterol and LDL-C reduction. We selected 32 well-defined F type II patients and for a prolonged period administered a combined diet-colestipol-nicotinic acid regimen to evaluate the effect of plasma cholesterol reduction on CAD.

PATIENTS AND METHODS

Patient Selection

Twenty-one male and 11 female CAD patients, ages 39 to 61 years, with F type II, who adhered to long-term diet-drug therapy, constituted the patient population of this report.

*From the Division of Cardiovascular Diseases, Department of Medicine, College of Medicine and Dentistry of New Jersey, Rutgers Medical School, Piscataway, NJ. Supported in part by research grants from Leola Detwiler Teaching and Research Fund: the American Heart Association, New Jersey Affiliate, and Somerset County Chapter. Manuscript received December 31; revision accepted April 16. Reprint requests: Dr. Kuo, Division of Cardiovascular Diseases, CMDNJ-Rutgers Medical School, Piscataway, New Jersey 08854

Diagnosis of F type II was made by consistently elevated serum cholesterol (>260 mg/dl), LDL-C (≥190 mg/dl), and triglyceride (>180 mg/dl) levels; demonstration of similar lipoprotein abnormality in first-degree family members in 26 of 32 patients; failure to respond to type II hyperlipoproteinemia diet, in six patients who had neither living nor hypercholesterolemic first-degree family members. Initially, each patient received a detailed description of the diet-drug program, information of known side effects of drugs to be used, and the purpose of the study, and was asked to sign an informed consent form approved by the Institutional Review Committee. Patients who could not commit themselves to long trial, women of child-bearing age, subjects with secondary hypercholesterolemia, and those who were receiving drugs and hormones with known effect on lipid metabolism were excluded from the study.

Diet

Eligible patients were kept on a regular diet without drugs known to have effect on plasma lipids for four to six weeks to obtain three baseline plasma lipid levels at two weekly intervals. Patients who could cooperate were given detailed instructions to start and maintain a low-cholesterol, low-saturated-fat, and low-simple-carbohydrate (“therapeutic”) diet for six weeks. The principal features of this diet are outlined in Table 1. Twenty-four-hour dietary recall and drug supply checking were made at periodic intervals throughout the treatment period as a means of improving adherence.

Methods

Serum lipid and lipoprotein analyses were made at six, four, and two weeks, and just before the patients began to take the drug treatment while they were maintained on the therapeutic diet. Immediately before the start of the drug treatment, each patient underwent the following: complete physical examination; ophthalmologic examination; ECG; chest x-ray; urinalysis; biochemical studies (fasting blood
FAMILIAL TYPE II HYPERLIPOPROTEINEMIA

Table 1—Principles of Low Cholesterol-Saturated Fat Diet

<table>
<thead>
<tr>
<th>Fats</th>
<th>Limit meat serving to 2-weekly, substitute it with fish and fowl. Substitute dairy fat &amp; non-dairy creamer with corn and safflower oil and unsaturated margarine. 35-40% of daily calories.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protein</td>
<td>Regular amounts. ~20% of total calories.</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>&lt;300 mg/day: avoid egg yolk, dairy products, organ meat. 35-40% of total daily calories.</td>
</tr>
<tr>
<td>Carbohydrate (CHO)</td>
<td>Moderately reduced (restrict simple CHO). 35-40% of total daily calories.</td>
</tr>
</tbody>
</table>

glucose, creatinine, SCOT, total serum bilirubin, alkaline phosphatase, uric acid, thyroxine, potassium, calcium, and phosphorus; and hematology studies (complete blood count, hematocrit reading, hemoglobin, platelet count, and prothrombin time). Microscopic examination and Sudan III stain were made on loose stool specimens.

History, physical examination, plasma lipoprotein analyses were done monthly. Biochemical and hematologic studies were repeated every three months throughout the treatment period. Serum total cholesterol (TC) and triglyceride (TG) concentrations were measured with automated procedures, standardized by the Center for Disease Control, U.S. Public Health Service. LDL-C was obtained by the difference between TC value and that of high density lipoprotein cholesterol (HDL-C) plus very low density lipoprotein cholesterol (VLDL-C). Statistical analysis of the differences between plasma lipid levels before and at various periods of diet-drug treatment was made by paired t test. A daily "cardex" system was used to determine the frequency of angina pectoris and diet-drug adherence. Exercise stress test on treadmill with standardized protocol was performed every four to six months. Colestipol, 10 g, was taken before meals three times a day.

This combination diet-colestipol treatment lasted for seven to 14 months. Nicotinic acid (NA) was added to the diet-colestipol regimen to accomplish a maximal reduction in the plasma lipids in each patient. The initial dose of the drug was 1.5 g/day given in three divided doses with meals. After the patient had surmounted the early-stage reactions, the NA was increased to 3 to 7 g/day over a period of two to three months depending on the plasma lipid response and the tolerance of the patient. Thirty-two patients kept a regular clinic attendance, and good diet-drug adherence records were kept in the study. Three patients who could not tolerate the initial drug reactions or keep regular clinic visits were excluded. Monthly follow-up, close physician-patient relationship, sharing of laboratory findings, drug supply count, and periodic dietary recall and review were used to boost long-term compliance.

Coronary arteriograms were performed in 28 symptomatic patients. Sixteen of them had second studies because they had completed three or more years of diet-combined drug treatment. Cine coronary arteriogram was performed by the selective dye injection technique of Sones. Segments of vessels without disease and their adjacent stenosis were estimated in the initial and repeated angiograms, using Sones’ catheter tip placed in the ostium as reference. Angiograms of each patient were reviewed by two of the investigators who had no knowledge of the clinical-laboratory status of the patient to obtain an unbiased opinion.

Clinical Studies

Twenty of the 32 patients had corneal arcus, tendinous xanthomata, xanthelasma or a combination of these findings. Twenty-one had angina pectoris, and 19 had one or more coronary occlusions with or without residual angina pectoris documented by history, ECG, exercise stress test, and coronary arteriogram. Six of those with CAD also had findings of brachiocephalic vascular disease but without ischemic complications.

RESULTS

Clinical Course

Substantial reduction of serum total cholesterol and LDL-C promoted slow resolution of the cutaneous and tendinous xanthomata. In 26 patients the symptoms and signs of CAD began to show improvement after three to four months of intensive medical therapy and weight loss ranging between eight to 25 lb. Subjective improvement, coupled with close follow-up visits and compliance boosting measures, encouraged close adherence to treatment, estimated at >85 percent on the basis of serum lipid values. Six poor responders with severe hypercholesterolemia (serum total cholesterol >500 mg/dl before institution of treatment) were resistant to the combined diet-drug therapy (average serum cholesterol reduction <15 percent of their mean baseline values). These six patients had five episodes of prolonged angina and ST changes in ECG, four recurrences of myocardial infarction as documented by serial ECG plus enzyme changes, and three episodes of pulmonary congestion during the follow-up period.

Table 2—Effects of Therapeutic Diet on Plasma Lipids of 32 Patients With Familial Type II Hyperlipoproteinemia

<table>
<thead>
<tr>
<th>Plasma Lipids, mg/dl (Mean ± SEM)</th>
<th>Baseline Before Diet</th>
<th>Therapeutic Diet</th>
<th>Result Δ and p†</th>
<th>% Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol</td>
<td>384.0 ± 14.1</td>
<td>334.9 ± 10.4</td>
<td>-49.1; P &lt;0.000</td>
<td>(-12.8)</td>
</tr>
<tr>
<td>Triglyceride</td>
<td>153.8 ± 9.8</td>
<td>128.0 ± 9.6</td>
<td>-25.8; P &lt;0.001</td>
<td>(-16.8)</td>
</tr>
<tr>
<td>LDL-Cholesterol</td>
<td>304.5 ± 14.4</td>
<td>263.4 ± 10.7</td>
<td>-41.1; P &lt;0.001</td>
<td>(-13.5)</td>
</tr>
<tr>
<td>HDL-Cholesterol</td>
<td>47.5 ± 1.7</td>
<td>47.0 ± 1.6</td>
<td>-0.5; NS</td>
<td></td>
</tr>
</tbody>
</table>

*Mean of three average values obtained in each patient.
†Paired t test.
‡Mean of values obtained in each patient at the end of six weeks.

CHEST, 79: 3, MARCH, 2017

Downloaded From: http://journal.publications.chestnet.org/pdffaccess.ashx?url=/data/journals/chest/21199/ on 06/05/2017
Table 3—Additive Effects of Colestipol to Diet on Plasma Lipids of 32 Familial Type II Patients

<table>
<thead>
<tr>
<th>Plasma Lipids, mg/dl</th>
<th>Therapeutic Diet Only</th>
<th>Colestipol Δ and p†</th>
<th>Result, (Mean ± SEM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol</td>
<td>334.9 ± 10.4</td>
<td>276.1 ± 7.6</td>
<td>-58.8; P &lt; 0.001</td>
</tr>
<tr>
<td>(6 wk)</td>
<td>(7-14 mos)†</td>
<td>(Mean ± SEM)</td>
<td>(17.5)</td>
</tr>
<tr>
<td>Triglyceride</td>
<td>128.0 ± 9.6</td>
<td>126.5 ± 9.3</td>
<td>-1.5; NS</td>
</tr>
<tr>
<td>LDL-Cholesterol</td>
<td>263.4 ± 10.7</td>
<td>202.5 ± 7.1</td>
<td>-60.9; P &lt; 0.001</td>
</tr>
<tr>
<td>HDL-Cholesterol</td>
<td>47.0 ± 1.6</td>
<td>48.6 ± 0.8</td>
<td>+1.6; NS</td>
</tr>
</tbody>
</table>

*Mean of values obtained in each patient at the end of six weeks.
†Mean of values obtained in each patient at the end of seven months.
‡Paired t test.

Effect of Treatment on Plasma Lipids

The therapeutic diet alone lowered the plasma TC, TG, and LDL-C of 32 patients with heterozygous F type II by 12.8, 16.8, and 13.5 percent, respectively, from their mean baseline values in six weeks (Table 2).

When the therapeutic diet was supplemented with colestipol, further significant reductions in plasma TC and LDL-C of these patients amounting to 17.5 and 23.1 percent, respectively, were observed in seven to 14 months. This combined treatment did not have any effect on either plasma TG or HDL-C (Table 3).

The additive hypolipemic effects of colestipol and NA and diet on the plasma lipids in this series of patients are presented in Table 4. In 28 to 102 months, their mean plasma TC, TG, and LDL-C were lowered to or near the normal ranges of 220.3, 83.9, and 145.8 mg/dl, respectively. NA administration increased the mean plasma HDL-C of these patients significantly from 47.0 to 57.2 mg/dl.

The total hypolipemic effect of diet, colestipol, and NA on this series of F type II patients is presented in Table 5. Compared with mean baseline values, the combined diet and two-drug treatment regimen lowered the total mean plasma TC, TG, and LDL-C by as much as 42.6, 45.4, and 52.1 percent, respectively, and at the same time raised the HDL-C level by 20.4 percent. If the six poor responders were excluded from the calculation, the mean serum LDL-C reduction and mean HDL-C elevation of the 26 treatment responders were estimated at greater than 54 and 21 percent, respectively.

Table 5—Total Effects of Diet, Colestipol, and Nicotinic Acid on Plasma Lipids of 32 Familial Type II Patients

<table>
<thead>
<tr>
<th>Plasma Lipids, mg/dl</th>
<th>Before Diet Drugs (28-102 mos)†</th>
<th>Result, (Mean ± SEM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol</td>
<td>384.0 ± 14.1</td>
<td>-163.7; P &lt; 0.001</td>
</tr>
<tr>
<td>(6 wk)</td>
<td>(14 mos)†</td>
<td>(42.6)</td>
</tr>
<tr>
<td>Triglyceride</td>
<td>153.8 ± 9.8</td>
<td>-69.9; P &lt; 0.001</td>
</tr>
<tr>
<td>LDL-Cholesterol</td>
<td>304.5 ± 14.4</td>
<td>-158.7; P &lt; 0.001</td>
</tr>
<tr>
<td>HDL-Cholesterol</td>
<td>47.5 ± 1.7</td>
<td>+9.7; P &lt; 0.001</td>
</tr>
</tbody>
</table>

*Mean of three average values obtained in each patient.
†Mean of values obtained in each patient at the end of 28-102 months.
‡Paired t test.

Effect of Diet-Drugs Treatment on Coronary Artery Lesion

Repeat coronary arteriograms were obtained on 16 patients who completed three or more years of treatment. In 12 responders to treatment, their original CAD had neither shown significant progression nor development of new lesions. Two examples are presented in Figures 1A, 1B, 2A, and 2B. Comparative studies of the pretreatment and posttreatment cine's failed to demonstrate a discernible degree of regression. Serial coronary arteriograms of four patients in the six poor responder group showed variable degrees of progression in their coronary lesions. The progressive coronary changes correlated well with the unstable clinical courses of these patients.
Severe stenotic lesion of one patient's left anterior descending artery and of circumflex artery show no significant change in 64 months.

**Side Effects**

Side effects of colestipol and NA occurred during the early stages of drug administration. In all patients the initial side effect of NA was flushing and pruritus. The drug also caused nausea, vomiting, diarrhea, or abdominal cramps in 11 patients. These reactions were minimized by forewarning, taking the drug with meals, and acclimation. More serious late effects were the development of hyperglycemia in three patients, hyperuricemia and gouty arthritis in three others, and hepatic dysfunction (as indicated by SGOT elevation) in two instances. These untoward reactions promptly subsided in all patients with interruption of drug administration. Readmin-istration of NA in smaller doses of 2 to 3 g per day was well tolerated.

The initial reactions of gritty taste, nausea, and bloating to colestipol disappeared after the patient had been receiving the drug for three to four weeks. Ten of the 32 patients complained of constipation. The symptom was relieved by a stool softener and by the development of tolerance to side effects with prolonged administration. Twelve patients complained of dry, scaly skin, which improved with lanolin ointment. During the prolonged period of drug treatment, none of our patients had signs and symptoms of cholelithiasis, hypoprothrombinemia, or hematologic or neurologic findings or both suggestive of vitamin or nutritional deficiency. Microscopic examination of stools made randomly did not reveal any evidence of malabsorption or steatorrhea. Except for the tendency to exacerbate hemorrhoidal bleeding, no gastrointestinal hemorrhage, obstruction, or cancer was observed. Some investigators

**FIGURE 1A (upper) and 1B (lower).** Severe stenotic lesion of one patient's left anterior descending artery and of circumflex artery show no significant change in 64 months.

**FIGURE 2A (upper) and 2B (lower).** Initial right coronary artery lesions of another patient show no significant progression in 62 months.
have observed a reactive increase in plasma triglyceride with resin treatment. We have circumvented this drug-induced hypertriglyceridemia by giving the therapeutic diet, which restricts excessive simple carbohydrate ingestion (Table 1).

DISCUSSION

A number of investigators have disclosed a close relationship between F type II, or familial hypercholesterolemia and accelerated development of CAD.10-12 Thus, F type II patients with CAD would provide the conditions for evaluation of hypcholesterolemic therapy for CAD. A defect in specific cellular LDL receptors has been demonstrated in patients with F type II disease,13 and it has been shown that the defect would stimulate overproduction and retard catabolism of LDL to raise the circulating LDL-C. Several investigators have used a combination of drugs to supplement dietary therapy to control excessive plasma LDL elevation in heterozygous F type II.14-16 In a preliminary report, Kane and associates16 reported that plasma LDL-C of most heterozygous F type II patients could be “normalized” by colesteol plus NA treatment. We have used the potent combination of drugs to evaluate the efficacy of long-term hypocholesterolemic therapy in the control of coronary atherosclerosis.

Colestipl resin binds bile acids in the intestines to form a nonabsorbable complex to increase fecal sterol excretion.17 The loss of bile acids increases cholesterol and LDL catabolism and stimulates increased cholesterol biosynthesis. Fortunately, in most cases the resin-induced increase in TC, and LDL-C catabolic rate is considerably higher than compensatory biosynthetic rate.

NA inhibits tissue lipolysis,18 reduces the rate of LDL and cholesterol synthesis, and increases cholesterol catabolism.19

Diet and colesteol treatment lowers the serum cholesterol primarily by decreasing the LDL-C fraction without altering the plasma HDL-C concentration.6 Addition of NA further reduces plasma TC, LDL-C, and TG levels, while raising the plasma HDL-C concentration. This finding confirms the report of Shepherd and associates.20 Thus, the combined diet, colesteol, and NA therapy results in a significant increase in HDL-C/LDL-C ratio. In view of reports that CAD is negatively correlated with plasma HDL, this modification in lipid-lipoprotein metabolism may be desirable. The bulk of evidence suggests that plasma TC and LDL-C should be reduced to and maintained at about 20020 and 150 mg/dl or lower, respectively, in order to obtain measurable beneficial effects.

In addition to clinical effect of the combined treatment, objective evidence obtained from repeated coronary angiograms in the present study show that coronary atherosclerosis was arrested by substantial degrees of serum lipid lowering, while coronary arterial lesions continued to progress in patients who did not show satisfactory response to therapy. A preliminary report by Nikkila et al8 also suggests that progression of coronary artery atherosclerosis is reduced more dramatically in patients with the greatest degree of plasma lipid lowering.

The present study suggests that if CAD progression could be arrested, compensatory mechanism(s) would develop, even in CAD-prone F type II patients, to improve the myocardial blood supply.

ACKNOWLEDGMENT: Best Foods, a unit of CPC North America, supplied us with corn oil for this study.

REFERENCES

3 Wagner WD, St Clair RW, Clarkson TB. Atherosclerosis regression in rhesus monkeys at plasma cholesterol levels achievable in man. Fed Proc 1976; 35:293
6 Kuo PT, Hayase K, Kostis JB, Moreyra AE. Use of combined diet and colesteol in long-term (7-73 years) treatment of patients with type II hyperlipoproteinemia. Circulation 1979; 59:199
10 Jensen J, Blankenhorn DH, Kornernp V. Coronary disease in familial hypercholesterolemia. Circulation 1967; 36:77
11 Slack J. Risks of ischemic heart-disease in familial hyperlipoproteinemic states. Lancet 1969; 2:1380
Management Update: Allergy, Immunology, Pulmonary Disease

This course, cosponsored by the National Jewish Hospital and Research Center/National Asthma Center, Denver, will be held May 8-9 at the University of Tennessee College of Medicine, Memphis, under the direction of Dr. Bernard M. Zussman. For information, contact: Ms. Grace Wagner, Continuing Medical Education, UTCHS, 800 Madison Avenue, Memphis 38163.