The Effect of Partial Ileal Bypass on Plasma Lipoproteins

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IN THE PROGRAM ON THE SURGICAL CONTROL OF THE HYPERLIPIDEMIAS

SUMMARY Plasma lipids and lipoprotein cholesterol concentrations were determined before and at 3 months and 1 year after partial ileal bypass surgery in 28 male survivors of first myocardial infarction (eight normolipidemic subjects and eight type II-A, two type II-B, eight type IV and two type V hyperlipoproteinemic subjects). All subjects had marked reductions in plasma total cholesterol (average 45% and 33% in the type V subjects and 37% and 31% in the other 26 subjects at 3 months and 1 year after surgery). Except for the two type V subjects, all had even more marked reductions in low-density lipoprotein (LDL)-cholesterol than in the total plasma cholesterol, averaging 51% at 3 months and 49% at 1 year after surgery. There were no significant changes in high-density lipoprotein (HDL)-cholesterol levels. The hypertriglyceridemic subjects had marked reductions in plasma triglycerides and very low density lipoprotein-cholesterol, whereas the normotriglyceridemic subjects (normals and II-A) had slight increases in these two measurements after surgery. Partial ileal bypass tends to normalize elevated plasma lipid and lipoprotein levels and results in a maximal lowering in LDL-cholesterol concentration without altering the HDL-cholesterol level.

CORONARY HEART DISEASE (CHD) is the most common cause of death in adults in the United States. The cause of this disease is not entirely established, but the significant underlying pathologic entity in nearly every case is atherosclerosis of the coronary arteries. Although the cause of atherosclerosis is not known, evidence from several scientific disciplines has led to the lipid (or sterol) hypothesis of atherogenesis, which implies that the plasma lipids (especially cholesterol) are directly involved in the pathogenesis of atherosclerosis.

For more than 25 years various therapeutic modalities (dietary modifications, lipid-lowering drugs and metabolic surgical procedures) have been used to lower the plasma concentrations of cholesterol and triglycerides, with the goal of reducing the risk of atherosclerotic cardiovascular disease. Partial ileal bypass surgery was introduced by our group in 1963 for the treatment of hyperlipidemia, and since then it has been shown to be the most effective single method of reducing elevated plasma lipid levels in patients with the common types of hyperlipoproteinemia. Information concerning the effect of this procedure on the major classes of plasma lipoproteins has not been reported. We are using this operation as the primary treatment modality in the Program on the Surgical Control of the Hyperlipidemias (POSCH), which is a multicenter secondary CHD intervention trial using maximal plasma lipid reduction in a test of the lipid-atherosclerosis hypothesis. This report on the changes in plasma lipids and lipoproteins observed in the first 28 male subjects who had partial ileal bypass surgery in the POSCH clinical intervention trial extends the knowledge of the effects of this lipid-lowering surgical procedure.

Methods

Subject Selection Criteria

The trial subjects must be 30-59 years old, either male or female, and must have sustained their first and only myocardial infarction (documented by history of ischemic cardiac pain lasting more than 30 minutes, elevated [over twice upper limit of normal value] serum enzymes [SGOT, LDH or CPK] with serial changes, and abnormal ECG indicative of infarction with serial changes) within 6-60 months at the time of entry into the trial. Plasma total cholesterol concentration must be 220 mg/dl or greater while on lipid-lowering dietary therapy (NHLBI type-specific diet instructions given by dieticians), and subjects cannot receive any other form of lipid-affecting therapy. Body weight must be no greater than 40% over ideal weight (Metropolitan Life Insurance Company tables), basal blood pressure must be less than 180 mm Hg systolic and 105 mm Hg diastolic, and the subjects must not have diabetes mellitus, hypothyroidism, nephrosis, hepatic disease, dysgamma globulinemia, or any other cause of secondary hyperlipoproteinemia. Subjects are excluded from the trial if they have unstable angina, heart failure, cardiomegaly, significant cardiac dysrhythmia, myocardial or aortic aneurysm, stroke, transient cerebral ischemic attacks, pulmonary insufficiency, renal insufficiency, pancreatitis, chronic hepatic or gastrointestinal disease, malignancy or any
Partial Ileal Bypass Surgery

The operation consists of a bypass of the distal 200 cm or one-third of the small intestine, whichever value is larger, with restoration of intestinal continuity by an end-to-side anastomosis of the proximal small intestine to the cecum. The details of this procedure have been reported elsewhere. Partial ileal bypass is not a weight-losing operation and should not be confused with the more extensive 90% jejunooileal bypass procedure that is used in the treatment of massive obesity. All patients are given parenteral vitamin B₁₂ supplements every 2 months after surgery.

Plasma Lipid and Lipoprotein Determinations

A plasma lipid profile is performed on each subject using three 14-hour fasting plasma samples obtained over 3–21 days. Venous blood samples (10 ml each) are mixed with solid disodium EDTA (14 mg) and the plasma is separated within 20 minutes of venipuncture and is kept at 4°C until the time of analysis (within 7 days). All lipid analyses are carried out in our Central Lipid Laboratory, which is standardized and certified by the Lipid Standardization Laboratory of the National Institutes of Health Center for Disease Control in Atlanta, Georgia. Plasma samples are examined (after standing overnight at 4°C) for turbidity and floating chylomicrons. Cholesterol and triglyceride concentrations are determined using the Technicon Autoanalyzer-II. Agarose gel electrophoresis is done on plasma and on the lipoprotein fractions using the BioRad BioGram-A system. High-density lipoprotein cholesterol (HDL) concentration is determined after precipitation of β lipoproteins (very low density lipoproteins [VLDL] and low-density lipoproteins [LDL]) with heparin and manganese chloride (2 ml plasma + 0.08 ml heparin solution [5000 units/ml] + 0.10 ml 1M MnCl₂ solution). Plasma (5 ml) is subjected to ultracentrifugation (Beckman L5-65 with 40.3 rotor) at d. 1.006 (18 hrs, 40,000 rpm, 4°C) and the VLDL-cholesterol concentration is determined in the top fraction (2.5 ml). The cholesterol in the bottom 2.5 ml fraction (made up of HDL and LDL) is then measured, and the LDL-cholesterol concentration is determined by subtracting the independently determined HDL-cholesterol from the bottom fraction cholesterol value. Agarose gel electrophoresis is done on the top and bottom fractions as well as on the HDL fraction for identification of the lipoprotein classes. If chylomicrons are present, a preliminary ultracentrifugation is done to remove the Sf > 400 particles (40.3 rotor, 19,000 rpm, 1 hour, 4°C). Lipoprotein phenotyping is done using the World Health Organization/National Heart, Lung, and Blood Institute system (with the ninetieth percentile for plasma cholesterol and the ninety-fifth percentile for plasma triglycerides as definitions of "hyperlipidemia"). The subjects are classified as normal, or types II-A, II-B, III, IV or V. This grouping of subjects is by phenotype and thus there may be heterogeneity within a group; no inference is made as to specific genetic states. We measured five variables in this study of the effects of partial ileal bypass surgery on plasma lipids and lipoproteins: plasma total cholesterol, plasma triglycerides, VLDL-cholesterol, LDL-cholesterol and HDL-cholesterol.

Statistical Methods

One-way analysis of variance tests were done using the mean values at each of the three time periods for each variable within three phenotype groups (normals, type II-A, and type IV) and within the overall group of 26 subjects (excluding the two type V subjects). The null hypothesis stated that the mean values for a variable were the same at the preoperative, 3 months postoperative, and 1 year postoperative time periods. In addition, this test was done on the average heights, weights, and ages at the initial study (before surgery) among the several subgroups of subjects.

The data presented in table 1 and figures 1 and 2 are the mean ± SE values for each of the plasma lipid and lipoprotein variables within the normal, type II-A and type IV phenotype groups and for the overall subgroup of 26 subjects (excluding type V). The type II-B and type V phenotype groups were not large enough to allow these calculations and for these two groups only the average values are given. The standard errors are given to permit the reader to make rapid visual determinations of significant differences between mean values at any two time periods (a significant difference [p < 0.05]) would be indicated by no overlap between mean values ± 2 SE). In the text the standard deviation is given for height, weight, and age values in order to describe the dispersion of the individual values for these measurements.

Tests of the difference between mean values for any variable at any two time periods were done using the equation for unpaired data; this is a conservative method for evaluating the data in this study. This test was done if the analysis of variance test showed a
TABLE 1. Plasma Lipids and Lipoproteins Before and at 3 Months and 1 Year After Surgery

<table>
<thead>
<tr>
<th>Group (n)</th>
<th>Plasma cholesterol (mg/dl)</th>
<th>LDL-cholesterol (mg/dl)</th>
<th>Plasma triglycerides (mg/dl)</th>
<th>VLDL cholesterol (mg/dl)</th>
<th>HDL-cholesterol (mg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal (8)</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Before</td>
<td>237.3 ± 4.6</td>
<td>171.8 ± 5.0</td>
<td>125.6 ± 11.2</td>
<td>18.7 ± 1.9</td>
<td>49.4 ± 3.4</td>
</tr>
<tr>
<td>3 mos</td>
<td>158.9 ± 6.8 (-33*)</td>
<td>80.5 ± 4.4 (-53*)</td>
<td>161.5 ± 13.2 (+29)</td>
<td>23.8 ± 3.2 (+27)</td>
<td>53.6 ± 3.6</td>
</tr>
<tr>
<td>1 yr</td>
<td>171.0 ± 11.1 (-28*)</td>
<td>105.0 ± 9.2 (-39*)</td>
<td>165.5 ± 18.9 (+32)</td>
<td>21.0 ± 2.7 (+12)</td>
<td>47.6 ± 3.0</td>
</tr>
<tr>
<td>II-A (8)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before</td>
<td>301.0 ± 13.0</td>
<td>236.0 ± 12.2</td>
<td>168.8 ± 14.0</td>
<td>25.3 ± 3.0</td>
<td>42.6 ± 2.7</td>
</tr>
<tr>
<td>3 mos</td>
<td>178.1 ± 15.1 (-41*)</td>
<td>117.1 ± 14.5 (-50*)</td>
<td>176.9 ± 20.0 (+5)</td>
<td>24.5 ± 4.9 (-3)</td>
<td>36.3 ± 3.0</td>
</tr>
<tr>
<td>1 yr</td>
<td>201.9 ± 18.8 (-33*)</td>
<td>130.8 ± 17.3 (-45*)</td>
<td>210.9 ± 33.0 (+25)</td>
<td>29.1 ± 7.2 (+15)</td>
<td>39.3 ± 2.8</td>
</tr>
<tr>
<td>II-B (2)</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Before</td>
<td>304</td>
<td>218.5</td>
<td>233</td>
<td>44.5</td>
<td>50.0</td>
</tr>
<tr>
<td>3 mos</td>
<td>178 (-41)</td>
<td>91.5 (-58)</td>
<td>246 (+6)</td>
<td>35.0 (-26)</td>
<td>51.6</td>
</tr>
<tr>
<td>1 yr</td>
<td>207 (-32)</td>
<td>117.5 (-46)</td>
<td>235 (0)</td>
<td>34.5 (-26)</td>
<td>58.5</td>
</tr>
<tr>
<td>IV (8)</td>
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<tr>
<td>Before</td>
<td>256.3 ± 8.1</td>
<td>157.3 ± 11.6</td>
<td>327.9 ± 49.9</td>
<td>57.6 ± 8.5</td>
<td>38.5 ± 2.5</td>
</tr>
<tr>
<td>3 mos</td>
<td>161.7 ± 7.5 (-37*)</td>
<td>85.1 ± 8.5 (-46*)</td>
<td>242.6 ± 19.1 (-26)</td>
<td>33.9 ± 5.5 (-41)</td>
<td>36.7 ± 2.8</td>
</tr>
<tr>
<td>1 yr</td>
<td>178.0 ± 9.8 (-31*)</td>
<td>98.4 ± 8.5 (-37*)</td>
<td>313.6 ± 20.1 (-4)</td>
<td>43.6 ± 4.0 (-24)</td>
<td>36.5 ± 2.2</td>
</tr>
<tr>
<td>V (2)</td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Before</td>
<td>355</td>
<td>78.0</td>
<td>1717</td>
<td>229</td>
<td>31.0</td>
</tr>
<tr>
<td>3 mos</td>
<td>197 (-45)</td>
<td>66.0 (-15)</td>
<td>933 (-46)</td>
<td>80 (-65)</td>
<td>24.0</td>
</tr>
<tr>
<td>1 yr</td>
<td>239 (-33)</td>
<td>78.0 (0)</td>
<td>896 (-48)</td>
<td>103 (-65)</td>
<td>33.0</td>
</tr>
<tr>
<td>All except V (26)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before</td>
<td>267.8 ± 7.2</td>
<td>190.7 ± 8.5</td>
<td>210.2 ± 22.0</td>
<td>34.7 ± 4.3</td>
<td>44.0 ± 1.9</td>
</tr>
<tr>
<td>3 mos</td>
<td>167.7 ± 5.7 (-37*)</td>
<td>92.9 ± 6.8 (-51*)</td>
<td>195.8 ± 11.8 (-6)</td>
<td>27.7 ± 2.5 (-20)</td>
<td>42.0 ± 2.5</td>
</tr>
<tr>
<td>1 yr</td>
<td>185.4 ± 7.7 (-31*)</td>
<td>97.4 ± 7.7 (-49*)</td>
<td>230.4 ± 7.7 (-49*)</td>
<td>29.6 ± 3.2 (-15)</td>
<td>42.5 ± 2.0</td>
</tr>
</tbody>
</table>

Values are average ± SE.
Values in parentheses represent percent change from preoperative value:
*p < 0.001.
†p < 0.05.
Abbreviations: LDL = low-density lipoprotein; VLDL = very low density lipoprotein; HDL = high-density lipoprotein.

significant difference among the mean values within a given subgroup of subjects for the three time periods. The null hypothesis states that there was no significant difference between the mean values for a given lipid or lipoprotein variable at two time periods (before vs 3 months or 1 year after surgery) within a specific group of subjects. Statistical significance was defined as being at the 95% level of confidence. In table 1 the magnitude of the changes in plasma lipid and lipoprotein measurements are given as the percent change of a postoperative mean value from the preoperative mean value within a group of subjects, and the above test was used to determine the significance of the observed percent changes after partial ileal bypass surgery.

Results

Twenty-eight male subjects were in this initial study. Eight were classified as normolipidemic, and eight as type II-A, two as type II-B, eight as type IV, and two as type V hyperlipoproteinemic subjects. The average age of the group was 50.3 ± 5.3 years (SD) (range 40–58 years) and there were no significant age differences between any of the five phenotype subgroups. The two type V subjects were more overweight (113.5 and 106.0 kg, average 38% over ideal weight) than the other 26 subjects (average 15% over ideal weight, average 84.0 ± 11.5 kg and 175.4 ± 6.0 cm), and there were no significant differences in height or weight among the normal, II-A, II-B, or IV groups. After surgery there was a slight reduction in the weight at 3 months, with a partial regain in weight at 1 year: the average ± SD values for the 26 nonobese subjects was 84.0 ± 11.5 kg before, 78.6 ± 11.4 kg at 3 months, and 79.7 ± 10.3 kg at 1 year after surgery. The magnitude of postoperative weight loss in the two overweight type V subjects was greater and the weight reduction was more persistent, averaging 109.8 kg before, 95.4 kg at 3 months, and 91.7 kg at 1 year after
FIGURE 1. Plasma and lipoprotein cholesterol concentrations (average ± SE) before, at 3 months and 1 year after partial ileal bypass. LDL = low-density lipoprotein; HDL = high-density lipoprotein; LP type = lipoprotein phenotype.

partial ileal bypass (the diet prescription in these overweight subjects included caloric restriction in order to effect weight loss).

None of the subjects had a diastolic blood pressure over 90 mm Hg. The systolic blood pressures were below 140 mm Hg in all except two subjects, whose blood pressures were 155/86 mm Hg and 160/89 mm Hg. All subjects were male Caucasians. Four had never smoked, and 12 of the remaining 24 had stopped smoking. The average smoking history for the group of 24 smokers was 37.6 pack-years. There were no significant differences in smoking history among the

FIGURE 2. Plasma triglycerides and very low density lipoprotein (VLDL)-cholesterol concentrations (average ± SE) before, at 3 months and 1 year after partial ileal bypass. LP type = lipoprotein phenotype.
five groups of subjects. One type II-A subject had tendon xanthomata (plasma cholesterol level on diet was 381 mg/dl) and a family history of hypercholesterolemia (mother and one brother). Another type II-A subject (plasma cholesterol 322 mg/dl on diet) had a family history of hypercholesterolemia (in a sister). A third type II-A subject had a positive family history of CHD (father had myocardial infarction at age 48 years) but no information on plasma lipid levels.

The analysis of variance tests demonstrated that there were highly significant \( p < 0.01 \) differences among the mean values at the three time periods for plasma total cholesterol and LDL-cholesterol within the normal, II-A, and IV phenotype groups and within the overall group of 26 subjects (excluding type V); there were no significant differences among the means for plasma triglycerides within any of these four groups or for VLDL cholesterol within the normals, type II-A, or 26 subject subgroup, but there was a significant difference \( p = 0.04 \) among the means for VLDL cholesterol in the type IV group.

Table 1 lists the average ± se values for each of the five plasma lipid parameters for each of the five phenotype groups before and at 3 months and 1 year after surgery; the average values for the overall group of 26 subjects (excluding the type V subjects, whose plasma triglyceride and VLDL cholesterol levels were very much higher than the other subjects) are shown at the bottom of this table. The average ± se values for plasma total cholesterol, LDL-cholesterol and HDL-cholesterol are illustrated in figure 1 for the normal, II-A, II-B, and IV phenotype groups. The bars at the right in this figure illustrate the average ± se values for the overall group of 26 nonobese subjects. We observed that each one of these 26 subjects had significant reductions in total plasma cholesterol and in LDL-cholesterol concentrations after surgery; the values 3 months after surgery were the lowest and there was a slight increase in the values from 3 months to 1 year after surgery. For each of these four groups there were highly significant \( p < 0.001 \) reductions in both plasma total cholesterol (upper part of figure 1) and LDL-cholesterol (middle part of this figure) after surgery. Although there were slight (but not statistically significant) increases in mean values from the 3-month period to 1 year after surgery, the 1-year values were still significantly \( p < 0.001 \) lower than the preoperative values.

The relative magnitude of the postoperative reduction was greater for LDL-cholesterol than for plasma total cholesterol for all phenotype subgroups except type V. The two type V subjects had preoperative LDL-cholesterol levels markedly lower than normolipidemic subjects; after surgery there was a slight reduction at 3 months but a return to preoperative levels at 1 year. These two were the only subjects who failed to maintain the marked LDL-cholesterol reduction after partial ileal bypass; however, they did have significant reductions in plasma total cholesterol after operation.

There were no statistically significant differences in the preoperative average HDL-cholesterol values among the normal, type II-A, II-B, or IV groups; the type V subjects had much lower preoperative HDL-cholesterol values than the other 26 subjects. Myers and co-workers\(^\text{a}\) have reported an inverse curvilinear relationship between HDL-cholesterol and serum triglyceride concentrations; the low HDL-cholesterol levels in our type V subjects reflect this relationship. After partial ileal bypass HDL-cholesterol values did not change significantly in any of the five subgroups in this study.

The effects of partial ileal bypass on plasma triglycerides and VLDL-cholesterol concentrations were more complex than the effects of this surgical procedure on plasma total cholesterol and LDL-cholesterol levels (table 1, fig. 2). There was a variable response among the subjects in a phenotype group: some had an increase, while others had a decrease after surgery. In the normotriglyceridemic subjects (normal and type II-A) about half of each group had an increase and the others had a decrease in plasma triglyceride level at 3 months after partial ileal bypass; a greater proportion of the type II-A subjects had increases in triglycerides at 1 year. Within each of these two groups there was considerable variability and the increases in average plasma triglyceride levels after surgery were not statistically significant (at the 95% level of confidence). In the hypertriglyceridemic subjects (type II-B and IV), a similar diversity of response to partial ileal bypass was observed, with about half of each group showing a decrease and half an increase in plasma triglycerides after surgery. Although plasma triglycerides were reduced an average of 26% at 3 months in the type IV group, the variability was such that this reduction was not statistically significant. In the two type II-B subjects there were no significant differences in triglyceride levels between any of the three time periods. Only in the two type V subjects did we observe consistently marked and sustained reductions in plasma triglycerides (which averaged 48% at 1 year after surgery).

The effects of partial ileal bypass on VLDL-cholesterol were variable among subjects within any given phenotype group. About half of the normotriglyceridemic subjects (normal and II-A) had an increase and half a decrease in VLDL-cholesterol level after partial ileal bypass. There were slight but not statistically significant increases in both of these two groups after surgery. Both type II-B subjects had a reduction in VLDL-cholesterol after surgery. Six of the eight type IV subjects had reductions in VLDL-cholesterol; the 3-month postoperative average value was significantly \( p < 0.05 \) lower than the preoperative value, but the 1-year value was not significantly lower than the preoperative value. The two type V subjects had marked reductions in VLDL-cholesterol after surgery (average 65% at 3 months and 55% at 1 year).

The magnitudes of the postoperative changes in plasma total cholesterol, LDL-cholesterol, plasma triglycerides, and VLDL-cholesterol are listed in table 1 (in brackets after the 3-month and 1-year average values). There were highly significant \( p < 0.001 \) and
consistent reductions in plasma total cholesterol level in all phenotype groups. There were highly significant and more marked reductions in LDL-cholesterol level in all groups except the type V group. Although plasma triglyceride and VLDL-cholesterol levels were elevated in the normal and type II-A groups, the changes were not statistically significant. Likewise, the reductions in plasma triglycerides in type IV and in VLDL-cholesterol in type II-B were not statistically significant. However, VLDL cholesterol was significantly reduced 3 months after surgery in the type IV group. In addition, both plasma triglyceride and VLDL-cholesterol levels were markedly reduced in the two type V subjects after partial ileal bypass.

Discussion

The lipid (or cholesterol) hypothesis of atherogenesis states that atherosclerosis is a disease of multiple causes in which altered lipid metabolism plays a crucial and operant role: The mass occurrence of atherosclerosis and clinical atherosclerotic cardiovascular disease in young and middle-aged adults has as its essential metabolic prerequisite the mass occurrence of elevated plasma cholesterol levels in the population. The positive association between elevated plasma cholesterol levels and the incidence of atherosclerotic cardiovascular disease does not appear to require further proof. However, what remains to be conclusively documented is the corollary of the lipid-atherosclerosis hypothesis: Does a reduction in plasma cholesterol level result in a decrease in the incidence or severity of atherosclerosis and clinically manifested atherosclerotic cardiovascular disease in man? Despite the lack of clear and convincing evidence demonstrating the beneficial effect of plasma lipid reduction in man, it has become standard medical practice to use dietary modification, hypolipidemic drug therapy, or partial ileal bypass surgery to achieve plasma lipid lowering in hyperlipidemic patients.

In 1963 partial distal ileal bypass was introduced for the treatment of hypercholesterolemia. Since then, it has been shown to be the most effective single therapeutic modality for plasma lipid reduction in patients with the common types of hyperlipoproteinemia. Plasma cholesterol reduction after this operation has been as much as 80% in some patients, with the average reduction being on the order of 40%. This cholesterol-lowering effect is in addition to any reduction obtained by prior dietary treatment. We have not observed any additional effect with the combined use of cholestyramine and partial ileal bypass. The effect of partial ileal bypass on the plasma triglyceride concentration appears to depend on the type of hyperlipoproteinemia. In normotriglyceremic patients it is elevated and in hypertriglyceridemic patients it is reduced. A similar, paradoxic elevation in plasma triglyceride levels in normotriglyceridemic patients has been noted with the use of the bile acid-sequestering agent cholestyramine. Information on the effect of partial ileal bypass on the plasma lipoproteins is limited. Lewis et al. noted a significant decrease in LDL (S, 0–12) in three hyperlipidemic patients. Strisower and coworkers reported an apparently permanent 40–50% reduction in LDL (S, 0–12) in one of two patients who had partial ileal bypass; the other patient had a similar initial reduction, but by 1 year after surgery more than half of this reduction was regained. The present study represents a detailed analysis of the effect of partial ileal bypass surgery on the three major classes of plasma lipoproteins in normolipidemic and hyperlipidemic man.

The rationale for using distal ileal bypass in the treatment of hyperlipemia is the establishment of a twofold drain on the body cholesterol pools: a direct drain resulting from increased fecal loss of normally absorbed dietary and endogenous (biliary) cholesterol, and an indirect or metabolic drain resulting from reduced bile salt absorption, which elicits a compensatory increase in hepatic conversion of cholesterol (derived from the plasma) to bile acids. We demonstrated that partial ileal bypass causes an average 60% reduction in cholesterol absorption, a 4.9-fold increase in fecal bile salt, a 2.7-fold increase in cholesterol excretion, and a three-fold increase in cholesterol biosynthesis with significant reductions in the exchangeable cholesterol pools. These metabolic changes appear to be permanent.

In addition to providing maximal plasma lipid reduction, partial ileal bypass effect is obligatory (cannot be altered by the patient) and permanent; we have observed no response escape in over 250 patients over a 15-year period. The procedure is safe (operative mortality is less than 0.5%) and it is associated with acceptable minimal side effects (change in bowel habit and need for parenteral B12), in contrast with the more extensive 90% jejunoileal bypass used in the treatment of massive obesity. Therefore, we use partial ileal bypass in combination with diet therapy to provide maximal lipid reduction in POSCH, which is the only secondary CHD intervention trial testing the lipid-atherosclerosis hypothesis. This project is a multicenter NHLBI-funded clinical trial designed to determine if plasma lipid reduction has a beneficial effect on atherosclerotic vascular disease and its clinical manifestations in subjects who have survived a first myocardial infarction.

The present report presents the effects of partial ileal bypass on the plasma lipids (total cholesterol and triglycerides) and the plasma lipoprotein (VLDL, LDL and HDL) cholesterol concentrations in the first 28 male subjects randomized to the surgical group in the POSCH clinical trial. All subjects had survived their first myocardial infarction, were not hypertensive or diabetic, and were either normolipidemic or had primary hyperlipoproteinemia; they were relatively healthy for CHD patients. Subjects were excluded if younger than 30 years or older than 59 years, so the average age of our subjects (50.3 years) only reflects the cohort of the general population that fits the various selection criteria used in this trial. We noted a slight (average 5 kg) loss of weight at 3 months.
after surgery, with a return toward preoperative values at 1 year. The two type V subjects were moderately obese (average 37% over ideal weight as compared to 15% for the others), and caloric restriction diets were prescribed to effect weight loss; they had greater and more sustained weight loss after surgery. These findings are similar to our previous experience in 101 patients, in which we noted that the patients who were of average weight tended to return to preoperative values within 1 year and those who were more overweight tended to reduce toward average weight and not regain the excess weight after surgery. This is probably the result of dietary modification recommended for the patients who were overweight, rather than any effect of partial ileal bypass. This is in contrast to the marked weight loss effect of the 90% jejunoileal bypass operation used in the treatment of massive obesity. Partial ileal bypass is not an effective weight-loss operation.

There was a definite reduction in plasma total cholesterol concentration in each subject after surgery, and the relative magnitude of the reduction was nearly the same in the several phenotype groups, averaging 37% at 3 months and 31% at 1 year. There were no statistically significant differences between the 3-month and 1-year postoperative cholesterol levels. The plasma cholesterol reductions were in addition to any hypocholesterolemic effects of the dietary treatment instituted before recruitment into the clinical trial at least 3 months before the baseline lipid determinations used in this report. These findings are similar to those we have previously reported in 126 patients studied for as long as 7 years after partial ileal bypass. The changes in LDL-cholesterol concentrations were even more marked than the plasma cholesterol changes; except for the two type V subjects, each of the other 26 subjects had a marked reduction after surgery, and the relative magnitude of these postoperative LDL-cholesterol reductions was similar in the several phenotype groups. The type V subjects had abnormally low LDL-cholesterol levels before surgery and there were only minor reductions at 3 months, with a return to preoperative values by 1 year after partial ileal bypass. However, these two subjects did show a persistent reduction in the total plasma cholesterol level after surgery.

The HDL-cholesterol concentration in the two type V subjects was considerably lower than in the other phenotype groups. The average preoperative value for the other 26 subjects (44 mg/dl) was similar to that reported in 50–59-year-old men in the Framingham study (44.8 mg/dl). After partial ileal bypass the HDL-cholesterol levels were not reduced significantly. This is important in view of the recent reports of the inverse relationship between plasma HDL-cholesterol levels and the incidence or prevalence of CHD, in these epidemiologic studies, middle-aged men with lower HDL-cholesterol levels had a higher incidence of CHD.

The effects of partial ileal bypass on plasma triglycerides and VLDL-cholesterol levels are more complex than its effects upon LDL- and total plasma cholesterol. The present study confirms our previous findings that in normotriglyceridemic subjects (normal and II-A phenotypes) plasma triglyceride levels tend to rise after surgery; however, this elevation does not extend into the frankly hypertriglyceridemic range in most patients. Not every subject demonstrated this effect, however, and nearly half of the 16 subjects had a decrease after surgery. A similar observation was made concerning the changes in VLDL-cholesterol level after partial ileal bypass in the normotriglyceridemic subjects. There was considerable variability within each phenotype group and the number of subjects was relatively small (eight in each group), which may well account for the lack of statistical significance for the modest average increases in plasma triglycerides and VLDL-cholesterol after surgery in the normal and type II-A groups. In hypertriglyceridemic subjects there was also a complex response to surgery. The two type II-B subjects had essentially no change in plasma triglycerides but did have an average 26% reduction in VLDL-cholesterol level. About half of the type IV subjects had decreased plasma triglycerides at 3 months but a smaller proportion had reduced values at 1 year; there was a statistically significant 41% reduction in VLDL-cholesterol concentration in the type IV group at 3 months after surgery. Both of the two type V subjects had marked reductions in plasma triglycerides and in VLDL-cholesterol level. The results in the hypertriglyceridemic subjects also confirm our previous findings of a reduction in plasma triglycerides after partial ileal bypass. Although the response of plasma triglycerides and VLDL-cholesterol to this procedure were not as consistent as the response of plasma total cholesterol and LDL-cholesterol, the net effect appears to be a slight elevation in triglycerides and VLDL in normotriglyceridemic subjects and a net reduction in these two levels in hypertriglyceridemic subjects. Many, but not all, of the hypertriglyceridemic subjects did have definite reductions in triglycerides and VLDL after partial ileal bypass.

The prospective epidemiologic studies have clearly demonstrated the positive association between plasma total cholesterol levels and the prevalence and incidence of CHD in the population of middle-aged adults. Plasma total cholesterol is the sum of the cholesterol in the three major plasma lipoprotein classes (VLDL, LDL, and HDL). LDL-cholesterol is directly related to CHD risk and HDL-cholesterol has been shown to be inversely related to this risk; multivariate analysis has shown that these two lipoprotein fractions exert an independent effect upon CHD risk. Thus, it would in theory be advantageous for subjects to have a high HDL level and a low LDL level. Whether any methods of achieving this will alter CHD risk is not known and is under investigation in the CHD intervention clinical trials. In the present study we have demonstrated that partial ileal bypass produces a marked and apparently permanent reduction in LDL-cholesterol, with no significant change in HDL-cholesterol. This procedure tends to normalize elevated plasma lipoprotein levels, and the effects
appear to be lasting. It remains to be seen whether the use of partial ileal bypass to effect maximal reduction in the atherogenic plasma lipids and lipoproteins will result in a reduction in CHD risk in man.

References


Appendix

Members of the POSCH Clinical Trial Study Group

The effect of partial ileal bypass on plasma lipoproteins.
R B Moore, H Buchwald and R L Varco

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