Effects and side-effects of partial ileal by-pass surgery for familial hypercholesterolaemia

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SUMMARY Ten patients with familial hypercholesterolaemia were subjected to partial ileal by-pass surgery. Plasma cholesterol fell by 41 and 38% and low-density lipoprotein cholesterol by 51 and 46% after six and 18 months respectively. High-density and very low-density lipoprotein cholesterol and plasma triglycerides were unaffected. Alanine aminotransferase increased transiently in half of the patients. Diarrhoea and slight steatorrhoea troubled most of the patients for the duration of the 18 months' period of observation. Other long-term side effects were slight but significant increase in the renal excretion of oxalic acid and reduction in the intestinal absorption of calcium. The study shows that this operation has metabolic side-effects that warrant continued medical care of these patients.

Partial ileal by-pass surgery is in general more effective than drug treatment of familial hypercholesterolaemia. It is also cheaper and poses no problems of patient compliance. Whereas much is known about the side-effects of the jejunoileal by-pass operation for obesity,¹ little is known about other than the most obvious side-effects of the partial ileal by-pass for hypercholesterolaemia. We have studied effects on plasma lipoproteins as well as several possible side-effects in patients operated on because of familial hypercholesterolaemia in the heterozygous form.

Methods

PATIENTS

Criteria for the diagnosis were (1) raised lipoprotein cholesterol concentration, (2) similarly affected first-degree relative, and (3) normotriglyceridaemia. Details of the patients are given in the Table. In all cases, family history indicated a high risk of premature ischaemic heart disease. They had all been instructed to follow a cholesterol-lowering diet,² but adherence was variable. They were asked to continue the diet postoperatively. Previous attempts at

pharmacological cholesterol reduction had been unsatisfactory, and, at the time of operation, they were not in treatment with lipid-lowering drugs.

The operation was performed essentially as described by Buchwald *et al.*³ The small intestine was transected either 200 cm from the ileocaecal valve or between the proximal two-thirds and distal one-third whichever procedure by-passed the largest segment. The distal ileal segment was closed, duplicated, and fixed to the mesentery to avoid invagination. The proximal segment, the jejunum, was anastomosed end-to-side to the ascending colon 6-8 cm distal to the ileocaecal valve (for details, see reference 3).

The patients were followed closely in the out-patient clinic and studied while they were in hospital before as well as six and 18 months after the operation. Of the 20 patients operated on to date, 10 have been followed for 18 months. The present study deals with these 10 patients, except as otherwise stated.

After an overnight fast, plasma lipoproteins were separated into very low-density lipoprotein, low-density lipoprotein, and high-density lipoprotein by ultracentrifugation of plasma at d 1.006 g/ml for 108×10^6 g $\times$ min, removal of very low-density lipoprotein as the supernatant material, and precipitation of low-density lipoprotein from the infranant material with heparin-manganese.⁴ Cholesterol⁵ and triglycerides⁶ were measured in

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Table Characteristics of patients

Patient	Sex	Age (yr) at operation	Ischaemic heart disease	Tendon xanthomas	Cholesterol (mmol/l plasma)*			Triglyceride (mmol/l plasma)†
					total	LDL	HDL	Total
KN	M	39	—	—	11.7	8.6	1.16	2.4
LT	M	29	—	—	11.1	10.1	0.75	0.9
PB	M	38	+	—	9.7	8.1	0.90	1.0
FP	M	49	+	+	10.5	10.2	0.88	1.1
SS	M	32	—	+	14.3	11.5	0.90	1.3
CS	M	50	—	+	11.9	9.8	1.19	0.9
IC	F	45	—	+	6.8	5.2	1.06	1.2
SN	F	41	—	+	15.9	13.4	1.63	1.3
SE	M	26	—	—	8.4	6.8	1.36	0.5
JV	F	33	—	—	14.9	10.5	0.83	2.8
Normal range					3.5–6.7	1.9–5.3	0.50–1.70	0.5–2.9

* 1 mmol/l = 38.7 mg/100 ml.

† 1 mmol/l = 88.5 mg/100 ml.

whole plasma and in the $d > 1.006$ g/ml infranatant before and after heparin-manganese treatment.

During a one-week hospital admission, the patients were studied on a controlled diet providing 70 g fat, 800 mg calcium, and 200 mg oxalic acid per 24 hours.⁷ After an equilibration period of three days, stools and urine were collected over four 24-hour periods, and the following procedures were performed: (1) stools were weighed, homogenised, and analysed for fat;⁸ (2) oxalic acid in urine was measured as described by Archer *et al.*,⁹ and intestinal absorption of oxalate was estimated by measurement of ¹⁴C in urine after oral administration of ¹⁴C oxalate,⁷ (3) absorption of calcium from the gut was determined by comparison of radioactivity in the forearm after an intravenous and subsequent 20 times larger peroral dose of ⁴⁷Ca as described by Curtis *et al.*,¹⁰ and (4) bone mineral content was estimated by bone densitometry – that is, measurement of absorption of ²⁴¹Am emitted gamma rays by a forearm.¹¹ Intravenous urography and cholecystography as well as routine blood analyses were performed by standard methods in the Departments of Radiology and Clinical Chemistry.

Statistical analyses were performed with Wilcoxon's rank sum test and Spearman's rank correlation test.

Results

Six and 18 months after the operation, the plasma cholesterol concentration had decreased significantly by 41 and 38% respectively, from a median of 11.9 to 7.1 and 7.4 mmol/l (Fig. 1). Low-density lipoprotein cholesterol decreased from a median of 10.4 to 4.9 and 5.4 mmol/l over the same

time periods, or by 51 and 46% respectively. Very low-density lipoprotein and high-density lipoprotein cholesterol were unchanged, as were total very low-density lipoprotein, low-density lipoprotein, and high-density lipoprotein triglycerides (Fig. 2). In two patients, marked but unquantified regression of xanthelasmata and tendon xanthomata occurred.

Moderate diarrhoea and steatorrhoea troubled most patients. This was reflected in significant increases in stool mass ($p < 0.01$) and faecal fat ($p < 0.05$) (median 427 g/24 hours corresponding to 209% increase in median value and 8 g/24 hours corresponding to 167% increase respectively after six months) that persisted after 18 months (436 g/24 hours corresponding to 216% increase and 9 g/24

Fig. 1 Cholesterol in plasma and in lipoprotein classes before and six and 18 months after partial ileal by-pass surgery. Medians and 10th and 90th percentiles. 1 mmol/l = 38.7 mg/100 ml.

Fig. 2 Triglyceride in plasma and in lipoprotein classes before and six and 18 months after partial ileal by-pass surgery. Medians and 10th and 90th percentiles. 1 mmol/l = 88.5 mg triolein/100 ml.

hours corresponding to 200% increase) (Figs. 3 and 4). In contrast, a small but significant reduction in body weight ($p < 0.001$) was transitory in most patients (Fig. 5). Thus, six and 18 months after the operation the median body weight had decreased by 6 and 1% respectively. Patients KN and JV, preoperatively moderately obese, sustained a substantial but desirable 13 and 21% loss of body weight, respectively.

As shown in Fig. 6, 24 hour renal excretion of

Fig. 3 Stool mass before and six and 18 months after partial ileal by-pass surgery.

Fig. 4 Faecal fat before and six and 18 months after partial ileal by-pass.

Fig. 5 Body weight before and six and 18 months after partial ileal by-pass surgery.

oxalic acid increased slightly but significantly ($p < 0.05$) in several patients. Six and 18 months postoperatively the median urinary oxalic acid was 54 and 51 mg/24 hours corresponding to a median increase by 86 and 76% respectively. Postoperative intestinal ^{14}C -oxalate absorption correlated with renal oxalate excretion ($r = 0.70$, $p < 0.05$). Eighteen months postoperatively, intravenous urography in these 10 patients revealed no instances of urolithiasis.

Absorption of calcium decreased significantly ($p < 0.05$) from median 17 to 14% (corresponding to a median decrease of 18%) after six months. The effect persisted at 18 months' follow-up (median 14%) (Fig. 7). The reduction in calcium absorption did not correlate significantly with increases in faecal fat excretion in individual patients ($r = 0.47$, $p > 0.05$). A decrease in bone mineral content in eight patients studied 18 months postoperatively was statistically insignificant (median - 2.1%). Serum calcium and alkaline phosphatase were unaffected.

No cholelithiasis developed in eight patients studied by peroral cholecystography both before and 18 months after the operation.

Serum alanine aminotransferase increased transiently in six of 10 patients during the first two postoperative months. Serum iron was somewhat reduced during the first months postoperatively, but it was thereafter normal with minor or no peroral

iron supplementation. Other routine blood variables were unchanged (haemoglobin, transferrin, albumin, prothrombin, bilirubin, sodium, potassium, magnesium, creatinine, standard bicarbonate).

Discussion

The lowering effect on plasma cholesterol of the partial ileal by-pass operation exceeds substantially that obtained in a closely similar group of patients treated with neomycin (23%) or cholestyramine (27%).¹² This agrees well with reports from other groups.¹³ The reduction in plasma cholesterol was entirely due to a fall in low-density lipoprotein, the class of lipoproteins specifically raised in familial hypercholesterolaemia. No changes occurred in total high-density lipoprotein, but our study does not preclude changes within this heterogeneous class of lipoproteins. The triglyceride-rich lipoproteins, very low-density lipoprotein, were also unchanged. In an early study,³ Buchwald *et al* reported a gradual increase in plasma triglycerides months and years postoperatively in patients with type IIa hyperlipoproteinaemia, but, in a later study,¹⁴ the effect of the operation on triglycerides and very low-density lipoprotein was more variable.

We made no attempt to evaluate the possible beneficial effects of the reduction in lipoprotein on

Fig. 6 Urinary oxalic acid before and six and 18 months after partial ileal by-pass surgery.

Fig. 7 Absorption of dietary calcium before and six and 18 months after partial ileal by-pass surgery.

the atherosclerotic process. This is the subject of a much larger, on-going, secondary prevention trial using the partial ileal by-pass operation.¹⁵ Our patients PB and FP died 1½ and three years after the operation with acute myocardial infarction. Both patients had suffered from ischaemic heart disease preoperatively as evidenced by prior myocardial infarction and typical angina pectoris, respectively. Other deaths did not occur.

Weight loss, although substantial in several patients, was not a clinical problem. In our patients, however, diarrhoea and steatorrhoea were not transient as found by some³ but not all¹⁶ previous workers. The severity of the problem varies and has caused one of our patients (IC) to request restoration of intestinal continuity, which promptly relieved her symptoms. In general, the problem, if present, can be managed by careful medication with antidiarrhoeal drugs, bile acid sequestering drugs to reduce bile acid concentrations in the colon, and low intake of dietary fat.

About half of the patients developed some degree of hyperoxaluria due to increased absorption of dietary oxalate.¹⁷ None of the patients, however, has to date developed urolithiasis.

Similarly, none of the patients studied by cholecystography 18 months after the operation had developed cholelithiasis. This agrees with findings by Buchwald *et al*³ and is consistent with the experience with bile acid sequestering drugs,¹⁸ the mechanism of action of which resembles that of the ileal by-pass.

The transient rise in serum alanine aminotransferase was less pronounced and of shorter duration than that observed after jejunoileal shunt for obesity,¹⁹ but it obviously suggests similar, transient liver damage. To our knowledge, no study has indicated long-term liver damage. Malabsorption of vitamin B₁₂ occurs after partial ileal by-pass,²⁰ and we therefore administer injections of vitamin B₁₂ every three months.

An important finding of the present study was reduced absorption of dietary calcium from the intestine. The reduction corresponded to that observed in obese patients subjected to jejunoileal by-pass.^{21 22} Results of bone densitometry 18 months postoperatively were inconclusive, and at this point we have considered it unwise not to assume that, with time, these patients will develop some degree of premature osteoporosis. To prevent this, if this is possible, we prescribe for our patients 1000mg calcium and 1800 units vitamin D (D₂ and D₃) daily.

Familial hypercholesterolaemia is a disease that often causes premature ischaemic heart disease and death. At present, the effective reduction of low

density lipoprotein concentrations that can be obtained with the partial ileal by-pass operation seems very desirable. It is apparent from this study, however, that the procedure has metabolic side-effects the importance of which is not necessarily minor. Moreover, it imposes bothersome gastrointestinal symptoms on the patients, and it does not free them from drugs and continued medical care. We continue to recommend it to patients with familial hypercholesterolaemia only if drug treatment has been tried and found ineffective, either because of the patient's inability to comply or because of lack of response despite good compliance.

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References

- 1 Andersen T, Juhl E, Quaade F. Jejuno-ileal by-pass for obesity – what can we learn from a literature study? *Am J Clin Nutr* 1980; 33: 440–5.
- 2 *The dietary management of hyperlipoproteinaemia*. U.S. Department of Health, Education and Welfare Publication no. 73–110. Bethesda, Md: National Institutes of Health, 1973.
- 3 Buchwald H, Moore RB, Varco RL. Surgical treatment of hyperlipidemia. *Circulation* 1974; 49: suppl. 1: 1–37.
- 4 Burstein M, Samaille J. Sur un dosage rapide du cholestérol lié aux α – et aux β – lipoprotéines du sérum. *Clin Chim Acta* 1960; 5: 609.
- 5 Abell LL, Levy BB, Brodie BB, Kendall FE. A simplified method for the estimation of total cholesterol in serum and demonstration of its specificity. *J Biol Chem* 1952; 195: 357–66.
- 6 Soloni FG. Simplified manual micromethod for determination of serum triglycerides. *Clin Chem* 1971; 17: 529–34.
- 7 Hylander E, Jarnum S, Keldsbo IL, Thale M. Standardized ('trifixed') diet in the study of chronic malabsorption syndromes. *Scand J Gastroenterol* 1978; 13: 423–31.
- 8 Kamer JH, Bokkel Huinink H, Weyers HA. Rapid method for the determination of fat in feces. *J Biol Chem* 1949; 177: 347–55.
- 9 Archer HE, Dormer AE, Scowen EF, Watts RWE. Studies on the urinary excretion of oxalate by normal subjects. *Clin Sci* 1957; 16: 405–11.
- 10 Curtis FK, Fellows H, Rick C. Estimation of human

- calcium absorption by external radioisotope counting. *J Lab Clin Med* 1967; **69**: 1036–41.
- 11 Madsen S, Ølgaard K, Ladefoged J. Degree and course of skeletal demineralization in patients with chronic renal insufficiency. *Scand J Urol Nephrol* 1978; **12**: 243–49.
- 12 Faergeman O. Effects and side-effects of treatment of hypercholesterolemia with cholestyramine and neomycin. *Acta Med Scand* 1973; **194**: 165–7.
- 13 Miettinen TA, Lempinen M. Cholestyramine and ileal by-pass in the treatment of familial hypercholesterolaemia. *Eur J Clin Invest* 1977; **7**: 509–14.
- 14 Moore RB, Buchwald H, Varco RL *et al*. The effect of partial ileal by-pass on plasma lipoproteins. *Circulation* 1980; **62**: 469–76.
- 15 Moore RB, Long JM, Matts JP, Amplatz K, Varco RL, Buchwald H, POSCH. Plasma lipoproteins and coronary arteriography in subjects in the program on the surgical control of the hyperlipidemias. *Atherosclerosis* 1979; **32**: 101–19.
- 16 Helsingen N, Rootwelt K. Partial ileal by-pass. Kirurgisk behandling av hyperkolesterolemi. *Nord Med* 1969; **82**: 1409–15.
- 17 Earnest DL. Enteric hyperoxaluria. *Adv Intern Med* 1979; **24**: 407–27.
- 18 Meinertz H, Færgeman O. Drugs affecting lipid metabolism. In: Dukes, MNG ed. *Side effects of drugs annual 2*. Amsterdam: Excerpta Medica, 1978.
- 19 Danö P, Nielsen OV, Petri M, Jörgensen B. Liver morphology and liver function before and after intestinal shunt operation for obesity. *Scand J Gastroenterol* 1975; **10**: 409–16.
- 20 Buchwald H. Vitamin B₁₂ absorption deficiency following by-pass of the ileum. *Am J Dig Dis* 1964; **9**: 755–59.
- 21 Danö P, Christiansen C. Calcium malabsorption and absence of bone decalcification following intestinal shunt operation for obesity. *Scand J Gastroenterol* 1978; **13**: 81–5.
- 22 Hylander E, Jarnum S, Kempel K, Thale M. The absorption of oxalate, calcium, and fat after jejunoileal by-pass. *Scand J Gastroenterol* 1980; **15**: 343–8.