JEJUNOILEAL BYPASS FOR MORBID OBESITY
- STUDIES OF THE LONG-TERM EFFECTS

by

Anders Sylvan

University of Umeå
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Anders Sylvan

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Jejunoileal bypass for morbid obesity - studies of the long-term effects

Anders Sylvan

From the Department of Surgery, University of Umeå, Sweden

Abstract

This study was aimed at investigating adverse and beneficial long-term effects of jejunoileal bypass (JIB) surgery in obese patients. The JIB was the first widely used surgical procedure for treatment of morbid obesity. The weight loss was remarkable, but the procedure was declared not appropriate for obesity surgery in the late 1970's. Serious late adverse effects such as liver cirrhosis and malignancies, have been postulated. Unexpectedly few studies have addressed these problems.

In the long-term follow-up of 87 uniformly operated patients, several persisting beneficial effects were found. The mean Body Mass Index was 41.5 kg/m² at the time of operation and 29.7 kg/m² sixteen years after the operation. Diabetes type II and hyperlipidemia, common in an obese population, was not found in this group. Reversals were performed in 3% of the patients in contrast to 20-30% in many earlier studies. Revisions performed in 8% of the patients due to excessive weight loss could have contributed to the good long-term outcome.

Percutaneous liver biopsies from 44 patients taken 14-20 (mean 17) years after JIB revealed normal or fatty liver, a lower degree of histological abnormalities than in 11 biopsies taken at the time of operations 1-14 (mean 6) years postoperatively. Liver cirrhosis seen early in one patient could not be found in the late biopsies.

Reduced activity of the fibrinolytic system has been shown to be a new cardiovascular risk factor. In 45 patients studied 14-20 years after JIB, the levels of both plasminogen activator inhibitor type 1 (PAI-1) and tissue plasminogen activator (tPA) were significantly lower than in a control group of 10 morbidly obese patients (PAI-1: 8.4 vs 32 U/mL, tPA: 7.2 vs 12 µg/L).

Bile acids are regarded as cofactors in the carcinogenesis in the colon and experimentally an increased frequency of malignant tumors has been demonstrated after JIB in carcinogen-induced rats. In 30 of the operated patients, colonoscopy with biopsy was performed 11-17 years after the operation. No evidence for malignant transformation was found as reflected by an absence of polyp formation, histologic dysplasia or aneuploidy in flow cytometric DNA analysis.

Eight hundred and thirty patients from 10 hospitals subjected to JIB were compared to 1660 controls with respect to malignant diagnosis over a 20 years period. No significantly increased risk for colorectal carcinoma could be demonstrated. However the overall risk for malignant disease was increased in the operated patients. The frequency of endometrial carcinoma was significantly elevated up to five years after the operation but was normal after that time.

In conclusion the postulated progress of serious adverse effects of JIB such as liver cirrhosis and malignant disease has not been possible to demonstrate. Several beneficial effects such as weight loss and reduction of cardiovascular risk factors have been found a long time after the operation.

Key words: Jejunoileal bypass, Obesity, Surgery, Liver biopsy, Fibrinolytic system, Colonoscopy, Flow cytometry, Cancer risk.
ABSTRACT

This study was aimed at investigating adverse and beneficial long-term effects of jejunoileal bypass (JIB) surgery in obese patients. The JIB was the first widely used surgical procedure for treatment of morbid obesity. The weight loss was remarkable, but the procedure was declared not appropriate for obesity surgery in the late 1970's. Serious late adverse effects such as liver cirrhosis and malignancies, have been postulated. Unexpectedly few studies have addressed these problems.

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ABBREVIATIONS

CI - confidence interval

BMI - body mass index

BPD - biliopancreatic diversion

FFA - free fatty acids

GB - gastric banding

GBY- gastric bypass

JIB - jejunoileal bypass

PAI-1 - plasminogen activator inhibitor type 1

RR - relative risk

SD - standard deviation

tPA- tissue plasminogen activator

VBG- vertical banded gastroplasty
This thesis is based on the following papers, which are referred to by their Roman numerals:

I Favourable Long-term Results with the End-to-Side Jejunoileal bypass.
Sylvan A, Sjölund B, Janunger KG.

II Liver Morphology in Long-term Follow-up After Jejunoileal bypass.
Sylvan A, Janunger KG, Stenling R.
Submitted.

III Normal Plasminogen Activator Inhibitor Levels at Long-Term Follow-up After Jejuno-ileal Bypass Surgery in Morbidly Obese Individuals.
Sylvan A, Rutegård JN, Janunger KG, Sjölund B, Nilsson TK.
Metabolism 1992;41:1370-2.

IV Colorectal Cancer Risk After Jejunoileal Bypass: Dysplasia and DNA Content in Longtime Follow-Up of Patients Operated on for Morbid Obesity
Sylvan A, Sjölund B, Janunger KG, Rutegård J, Stenling R, Roos G.

V Jejunoileal Bypass and Malignant Tumors.
Sylvan A, Janunger KG.
In manuscript.
BACKGROUND

Obesity
Obesity is defined as an abnormal state of health in which there is an excess of body fat. When defined as a body mass index (BMI) > 30 kg/m$^2$, the prevalences are 7-8% in Sweden and 12% in the United States. Morbid obesity is often defined as an overweight > 100 pounds (45 kg) or an excess weight of 170% or more. Obesity is associated with an increased prevalence of cardiovascular risk factors such as hypertension, diabetes, hypofibrinolysis and lipid disturbances. Dieting or medical treatment of morbid obesity has by now proven to be an unsuccessful way of reducing weight in the long-term.

Historical viewpoint
Victor Henriksson, a Swedish surgeon, in 1951 was the first to report on an attempt of surgery for weight reduction. He resected 105 cm of the ileum in a young overweight woman. This, however, did not have the desired effect as her bodyweight had increased by 2.2 kg within fourteen months. Previous anecdotal reports on unvoluntary weight reduction after massive enteric resections have been reported after trauma, arterie occlusions or ileus.

Animal experiments, mainly on dogs, were performed as early as 1910. Flint found a pronounced compensatory increase in villous height, length and diameter of the small intestine in continuity after bypassing the content to a shorter passage. More systematic studies on bypasses on dogs were performed by Kremen in the early 1950s. This led to the first series of jejunocolic bypass on humans reported by Payne 1963. This shunt turned out to be a metabolic disaster with severe electrolyte disturbances and even deaths. From this initial experiment on humans, the jejunoleal bypass was developed.

The bypass was constructed of 14 inches of proximal jejunum anastomosed end-to-side to the distal four inches of ileum, leaving a blind loop of 85-90% of bypassed small intestine. In 1969 the results of the first patient series of 80
Figure 1. Different bypass procedures.
patients were reported on. The method soon became popular throughout the world resulting in numerous reports on the different effects of the shunt. Failure in weight reduction found in some patients was explained by reflux of ileal content into the blind loop. In view of this some surgeons advocated an end-to-end bypass where the blind loop was drained into the colon. In two randomised studies the two methods had a similar weight reducing effect but the liver biopsies showed more pronounced fatty infiltration after end-to-end than end-to-side JIB. An increasing stream of reports on adverse effect after all types of JIB induced the development of new gastric restrictive methods and gastric bypass in obesity surgery. The latest innovation in this field was the biliopancretic diversion, designed by Scopinaro at Genua in the beginning of the 1980s (figure 1).

**Effects on weight**

A number of mechanisms can account for the weight loss seen after JIB. The bypass was thought to cause weight loss primarily by pure malabsorption since the small intestinal absorptive surface will be reduced by 85%. This results in a short transit time leading to loss of fat and carbohydrates with the stools. Later studies on humans and animals also showed a reduction in food intake after JIB which can be an expression of earlier satiety. Furthermore, the shunt can act as a behaviour modifier as excessive intake of fat causes foul smelling diarrhoea.

The JIB-induced weight reduction is pronounced during the first year, but little weight loss is seen after 18-24 months. Compensatory extensive hypertrophy of the small intestine in continuity halts the negative energy balance.

Weight loss can be expressed as:

1) reduction of body weight (kg)
2) reduction of Body Mass Index (BMI) (kg/m²)
3) reduction of initial body weight (%)
4) reduction of initial excess weight (%) based on Metropolitan life table of ideal weight.
Several studies have shown a mean reduction of 35-40% of initial bodyweight or a 70-80% reduction of initial excess weight two years after the operation.\textsuperscript{51,112} Few studies on long-term (>10 years) weight development are published.\textsuperscript{101,133}

**Beneficial metabolic effects**

Several beneficial effects have been reported after JIB and weight reduction. Starting from insulin resistance associated with the obese state, a reduction of the levels of plasma insulin, blood glucose and serum lipids have been reported.\textsuperscript{1,55} For the treatment of familiar hypecholestreolemia a partial JIB, with no weightreducing capacity, has been developed.\textsuperscript{22} Also, the weight loss has been observed to reduce hypertension\textsuperscript{55}

**Adverse metabolic effects**

The knowledge of the metabolic response to the JIB grew parallel to the increasing number of reports on adverse effects. Diarrhoea is prone to develop a few days after JIB surgery. It soon reaches a peak in frequency, in some cases up to 20 stools daily.\textsuperscript{82} After three months a frequency of three to six stools has been reported to decrease to a median value of about three stools after one year. Electrolyte disturbances, in form of low levels of potassium, magnesium or zinc was soon noted as a result of the initial diarrhoea period.\textsuperscript{56} It generally subsides when maximal compensatory intestinal hypertrophy is reached. An impaired uptake of vitamin B\textsubscript{12} will in most cases persist and require supplementation.\textsuperscript{30}. Calcium metabolism may be disturbed due to malabsorption of vitamin D and calcium as well as enteral excretion of calcium after saponification of bile salts.\textsuperscript{58} This is seldom a clinical problem since obese persons have an elevated content of skeletal calcium.\textsuperscript{29} However, a few cases with osteomalacia have been reported.\textsuperscript{80}

Due to unchanged high fecal bile acid saponification, an increased enteric uptake of oxalate can lead to the formation of renal stones.\textsuperscript{36,49,56,69} Arthralgias caused by circulating immune complex are sometimes found together with skin
lesions and fever. Bypass enteritis is defined as abdominal pain, fever and diarrhea responding to antibiotic treatment, preferably with an anaerobic spectrum. Rare conditions as intestinal tuberculosis, pneumatosis cystoides have been reported in conjunction with JIB but no rational for underlying mechanisms have been postulated. Gall stone formation and hair loss were early attributed to the operation but these conditions are observed after any rapid substantial weight loss irrespective of dieting or obesity surgery.

Liver disease

Shortly after introduction of the jejunocolic bypass, a number of adverse effect on the liver were observed. Several reports after JIB have contributed to characterise the type of potential liver disease after JIB. Two different patterns can be identified.

1) Liver steatosis, observed in 80-90% of obese subject, may aggravate shortly after JIB surgery during the most intensive weight losing period. This steatosis regresses later in some cases but in others progressively become worse leading to fatty fibrosis and eventually cirrhosis. During the early period elevated levels of transaminases and alkaline phosphatase in serum are observed in a substantial proportion of patients. The levels often normalize spontaneously over a period of 18-24 months. However, attempts at identifying serum markers of progressive liver disease have failed.

2) Liver failure, both in a rapid form seen early after surgery and a late more chronic or slow form late have been observed. The condition is characterised by fatigue, oedema and hypoproteinemina, in advanced cases with jaundice, impaired coagulation or cerebral confusion. The condition is lethal if untreated. Both antibiotic treatment or parenteral low calorie aminoacid infusion have proved successful and may reverse the condition completely.
Intestinal adaptation and carcinogenesis

Bypassing the small intestine leads to an extensive hypertrophy of the intestine in continuity and atrophy of the blind loop. This was first described in dogs by Fint as an increase in villous height, diameter and length of the intestine.\(^4\) These findings were confirmed in humans after JIB surgery.\(^39,118\) The effects on the colon were initially not studied in humans. Studies on rats showed an increase in proliferative activity, total length and weight of the colon after JIB.\(^19\) It was hypothesised that the increase in exposure of the colonic mucosa to bile acids could eventually lead to malignant transformation.\(^20\) This theory was supported by the findings that carcinogen-induced rats developed more colorectal tumours after JIB than did shamoperated rats.\(^79,100,113\) Twenty-five years after the onset of the JIB operations there is only one case report of JIB-associated colon cancer in the literature.\(^69\)

Surgical complications and repair

Acute surgical complications include intestinal obstruction due to a narrow anastomosis or leakage leading to formation of an intraabdominal abscess.\(^12,40,104\) Intussuseption may occur even a long time after the operation if the blind loop is left in the abdominal cavity without fixation.\(^119\) Incisional hernias are reported in frequencies between 10-12%.\(^47,83,137\) Plastic surgery of the abdomen, breasts, thighs and upper arms can in some cases become necessary due to excessive skinfolds after mobilisation of subcutaneous fat.\(^89\)

Mortality

After the first decade of bypass surgery the mortality rate, early and late, was reported to be 4.3%.\(^8\) A total of 6222 patients were included in a literature study by Andersen. The study showed that the cause of 218 deaths was liver disease (32%), pulmonary embolism (18%), gastrointestinal complications (12 %), cardiac disease (8%), respiratory disease (4%) and miscellaneous (26%). The high rate of pulmonary embolism, is probably due to the ignorance of the value of thromboprophylaxis. Mortality rates of 0-1% have been reported in some patient series in the last decade.\(^34,35,69\)
Current opinion
Due to the great number of adverse effects reported after JIB, this operation is not included in the NIH Consensus 1991 and, therefore, not in use in USA. A few centres in northern Italy have reported patient materials operated during the 1980s. They have observed less adverse effects than were reported in the 60s and 70s. In Sweden the JIB is still performed by some surgeon.

AIMS
The current literature on jejunoileal bypass arguing for the dismissal of the operation in obesity surgery are partly based on short-term follow up and selected patient materials. Major arguments proposed include; the risk of developing liver cirrhosis, metabolic failure, renal calcinosis, osteomalacia and colon cancer.

Apart from the weight reduction, few long-term beneficial effects of the bypass have been studied.

The aim in the present study was to study the overall outcome after end-to-side jejunoileal bypass in a long-term follow-up on a consecutive patient series with respect to:

☐ weight reduction

☐ morbidity and mortality

☐ the development of liver disease, especially the risk for liver cirrhosis

☐ the effect on cardiavascular risk factors and diabetes in the metabolic syndrome

☐ the risk of malignant disease with special regard to colorectal cancer
Figure 2. Hospitals participating in Paper V
MATERIAL

Paper I. Eighty-seven, morbidly obese patients, 8 males and 79 females, operated on with end-to-side JIB at Örnsköldsvik county hospital between 1969 and 1977 were investigated. The preoperative weight was $112\pm 17$ (mean±SD) kg. Mean age at operation was 35 years (range: 18-56).

Paper II. Of fifty patients from the original series, 11 had liver biopsies taken at abdominal operations $6.1 \pm 5.4$ years (mean±SD) after JIB and 44 had percutaneous liver biopsies taken $17 \pm 1.5$ (mean±SD) years after JIB. In five patients both types of biopsies were performed.

Paper III. Forty-five patients from the original series were analysed for fibrinolytic variables $15.6 \pm 1.6$ years (mean±SD) after JIB surgery. They were aged $52 \pm 9.2$ (mean±SD) years and had a weight of $79.4 \pm 10.3$ (mean±SD) kg. These patients were compared to a control group consisting of 10 patients on the waiting list for obesity surgery aged $36 \pm 8.6$ (mean±SD) years with a weight of $124.5 \pm 23.6$ (mean±SD) kg.

Paper IV. Thirty patients from the early part of the original series were investigated by colonoscopy $13.9 \pm 1.5$ (mean±SD) years after JIB.

Paper V. A total of 830 patients in consecutive series from 10 hospitals in Sweden, 669 females and 161 males, operated on with JIB between 1969 and 1989 were investigated for risk of cancer. A control group consisted of 1660 persons from the national personal number register matched for sex, birthdate and birthplace.
Figure 3. Jejunoileal bypass (end-to-side) according to Payne and DeWind.
METHODS

Operation (I)
All 87 patient were originally operated on with the end-to-side jejunoileal bypass as described by Payne and DeWind in 1969. They were all operated by the same surgeon in a uniform way anastomosing the proximal 35 cm (14 inch) of the jejunum end-to-side to the distal 10 cm (4 inch) of the ileum. The blind loop of small intestine was closed and left in place (figure 3).

Clinical follow-up (I)
The patients were clinically checked up 3-4 times during the first postoperative year, thereafter once yearly or when the clinical situation required it. These check-ups were initially done by the surgeon who performed the operation but later on by his successors. When the situation became stable after the first five years, the routine visits were made every second or third year. The check-up included a clinical examination, laboratory tests and data regarding body weight and bowel habits. Since there was no standard protocol used at the start of these operations, the collection of laboratory data was not systematic. Retrospective analysis of patient records were done 1986, 1990 and 1994 apart from a complete patient survey with blood chemistry during 1988-89 (table 1).

Table 1. Antropometric and metabolic variables at follow-up.

<table>
<thead>
<tr>
<th>Length</th>
<th>S-Alkaline phosphatase</th>
<th>S-Creatinine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight</td>
<td>fP-Cholesterol</td>
<td>S-Magnesium</td>
</tr>
<tr>
<td>Waist</td>
<td>fP-Triglyceride</td>
<td>S-Zinc</td>
</tr>
<tr>
<td>Hip</td>
<td>P-Insulin</td>
<td>S-Ferritin</td>
</tr>
<tr>
<td>Waist/Hip-ratio</td>
<td>B-Glucose</td>
<td>P-PAI-1</td>
</tr>
<tr>
<td>B-Hemoglobin</td>
<td>S-Calcium</td>
<td>P-tPA</td>
</tr>
<tr>
<td>S-B_{12}</td>
<td>S-Phosphate</td>
<td>P-vWF</td>
</tr>
<tr>
<td>S-ASAT</td>
<td>S-Natrium</td>
<td>P-Antitrombine</td>
</tr>
<tr>
<td>S-ALAT</td>
<td>S-Potassium</td>
<td>S-Bile acids</td>
</tr>
<tr>
<td>S-Bilirubin</td>
<td>S-Albumin</td>
<td>S-Procollagen-III-peptide</td>
</tr>
<tr>
<td>S-GGT</td>
<td>S-Protein</td>
<td>B-Sedimentation rate</td>
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</table>
Liver biopsies (II)

Liver biopsies were not performed peroperatively when the JIB was performed. One reason for this was that the effects of the JIB on the liver were not known when the operation was introduced in 1969. When the patients operated on with JIB for different reasons had a second abdominal operation, open wedge liver biopsies were taken. After more than a 15 year mean observation period with no case of progressive clinical liver disease, a percutaneous liver biopsy study was conducted on all available patients.

The percutaneous biosies were performed by one radiologist with the aid of ultrasonography. A 0.9 mm needle (Biopty-CUT, Radiplast, Uppsala, Sweden) was used.

All biopsies, open and percutaneous, were fixed in formalin, imbedded and stained with hematoxylin-eosin. The coded specimens were all examined by one pathologist. On a four-graded scale the degree of fatty infiltration, focal necrosis, focal inflammation, portal inflammation, central fibrosis, sinusoid fibrosis, protal fibrosis and bridging fibrosis were evaluated and classified according to the criteria published by Adller and Schaffner into one normal and four pathological groups (Table 2).

<table>
<thead>
<tr>
<th>Table 2. Liver disease classification according to Adler and Schaffner²</th>
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<tbody>
<tr>
<td><strong>Group I. Fatty Liver:</strong> Fat deposition with or without mild focal necrosis and inflammation.</td>
</tr>
<tr>
<td><strong>Group II. Fatty hepatitis:</strong> Fat deposition with moderate focal necrosis, inflammation, portal inflammation but no or only mild portal fibrosis.</td>
</tr>
<tr>
<td><strong>Group III. Fatty fibrosis:</strong> Fat deposition and hepatitis with moderate or severe portal fibrosis sometimes with septums bridging between portal and central fields.</td>
</tr>
<tr>
<td><strong>Group IV. Fatty Cirrhosis:</strong> Fat deposition and hepatitis with fibrotic septums arranged around regenerative nodules of parenchyma.</td>
</tr>
</tbody>
</table>
The fibrinolytic system (III)
The activity of the fibrinolytic system in a subgroup of 45 patients was investigated. After an overnight, fast blood samples were collected between 8.00-10.00 a.m. Plasminogen activator inhibitor type 1 activity and tissue plasminogen activator were analyzed. Other variables studied were insulin, glucose, cholesterol, triglycerides, BMI, all defining different aspects of the metabolic syndrome. The results were compared to a control group of morbidly obese persons.

Colonic mucosal biopsies (IV)
As a part of the clinical follow-up, 30 patients were offered and accepted a colonoscopy. Mucosal biopsies were taken from six defined locations of the colon. The following parameters were studied:
1) Macroscopic appearance - number of polyps or other lesions were noted.
2) Histology - biopsy specimens were fixed in formaldehyde, paraffin-embedded, sectioned and stained with hematoxylin-eosin. Signs of epithelial dysplasia was evaluated by a single pathologist (Dr R Stenling).
3) DNA analyses on fresh-frozen mucosal biopsies were investigated by flow cytometry to access the occurrence of aneuploidy.

Cancer risk (V)
We studied consecutive patient series from 10 different hospitals, known to have performed the majority of JIB surgery in Sweden during the study period 1969-1989. Eight hundred and thirty patients were found. Data on the surgical method, year of surgery and year of eventual reversal could be found for 800 (96%) patients. The patients were matched with a pair of controls selected by adding and subtracting two to the national personal register number. The Cancer Registry of the National Health and Welfare and the Causes of Death from the National Central Bureau of Statistics were analysed with regard to diagnosed malignancy, eventual death and if so the cause of death for a total of 2,490 persons.
Statistical methods

In paper III the difference between the two studied groups were tested using Wilcoxon rank sum test. Correlations and multiple regression of variables in the metabolic syndrome were calculated using a computerized statistic program (Status 2, Foresco, Umeå, Sweden).

In paper V the statistical analyses of data were based on the Mantel and Haenszel method for the calculation of odds ratio. The 95% confidence intervals (CI) were calculated according to Cornfield as expressed by Breslow and Day.
RESULTS AND DISCUSSION

Beneficial effects

Weight (I)
The weight reduction potential of the JIB is well recognised.\textsuperscript{13,133} In the present series of patients the initial weight of 112±17 kg (±SD) was reduced to 72 ±12 within two years. A minor weight gain was noted at the long term the follow up. At 16 years the mean weight was 78±11 kg (±SD). Weight reduction expressed as excess weight % loss or in terms of BMI reveal that the ideal weight has not been reached (figure 3, 4). The cure rate, defined as less than 40% excess weight, was 88% at 4 years and 75% at 16 years after the operation. Others have also shown similar long-term results after JIB and biliopancreatic diversion respectively.\textsuperscript{101,108} Comparable long-term results (> 10 years ) after gastric restrictive or gastric bypass procedures is still lacking in the litterature.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure3.png}
\caption{Weight development after JIB expressed as body mass index (mean±SD).}
\end{figure}
The primary goal of obesity surgery is weight reduction. The majority of the different surgical procedures in obesity surgery that have been presented during the last twenty years lead to an appreciable weight reduction during the first two years. However, in the long-term several gastric restrictive procedures (horizontal gastroplasty, gastric wrapping, gastric banding) have showed inadequate weight maintenance in the long run. Mason has found a considerable failure rate at 5 years follow-up after VBG, 49% of 313 patients had less than 50% excess weight loss (EWL).  

![Figure 4. Weight development expressed as excess weight % loss. (Mean+SD).](image)

When comparing the adverse effects of a bariatric procedure it is relevant to refer to methods with similar weight reduction. Gastric procedures with few adverse effects but inadequate weight loss is not comparable to malabsorptive procedures with long-standing weight reduction.

**Metabolic syndrome (III)**

Obesity is known to be linked to other pathological findings such as hyperinsulinemia, diabetes, hypertonia, triglyceridemia and hypofibrinolysis, together constituting the metabolic syndrome. Although the ideal weight was seldom reached after JIB in these morbidly obese patients
we, found normal blood values for insulin and glucose in all investigated patients. No patient with diabetes was found at their latest follow up. Preoperative values were not known for the patients in this series. A frequency of 1-2% diabetes is to be expected in a population with a mean age of 50 years and normal weight. Considering that these patients are still slightly obese an even higher prevalence of diabetes could be expected. Triglycerides and cholesterol were also within the normal range for all patients at their latest follow up.

A reduced activity in the fibrinolytic system expressed as high levels of plasminogen activator inhibitor type 1 (PAI-1), the inhibitor of tissue plasminogen activator (tPA), is regarded as the strongest single predictor for cardiovascular events after survival of a myocardial infarction. In the present study we investigated the fibrinolytic parameters in 45 previously operated patients and 10 controls. The values of PAI-1 and tPA were 15 years after the operation significantly lower than for morbidly obese controls, (PAI-1: 8.4±8.0 vs 32.0±21.6 U/mL p<0.001; tPA: 7.2±4.9 vs 12.0±5.2 µg/L p<0.003). The majority of JIB patients had PAI-1 and tPA values within normal range in contrast to the elevated levels seen in the obese control group (figure 5). This observation can partly explain why cardiovascular disease was almost absent in the operated group.

**Figure 5.** Distribution of PAI-1 levels in JIB-operated patients and controls. (Normal value: < 10 U/mL)
Hypertonia, diabetes and hyperlipidemia can be controlled by pharmacological treatment. Up to now, no medical treatment has been able to reduce elevated PAI-1 and tPA levels. Weight reduction in the range of 2-9 kg after dieting has been shown to reduce PAI-1 by 21-45%. The present study indicates that weight loss after JIB has a potential of normalising hypofibrinolysis. This has been confirmed in a study of morbidly obese patients with a mean loss of 64 kg after VBG operation which lead to a reduction of 68% of PAI-1. Our observation that the majority of patients have metabolic values within normal range in spite of a mild overweight implies that the effect of JIB on metabolism is not only linked to weight reduction. This phenomena could partly explain the favourable outcome on cardiovascular events in the POSCH-study. They found that a partial ileal bypass operation on hypercholesterolemic patients who had survived one myocardial infarction lowered the risk for new cardiovascular events compared to a pharmacologically treated group. Partial ileal bypass is known to lower hypercholesterolemia but does not induce weight reduction.

Adverse effects

Electrolyte disturbance (I)
Low serum values of potassium and magnesium clinically presenting as weakness, cramping or tetanus required supplementation in 25% of the patients in the early postoperative period. This was probably due to malabsorption. When maximal intestinal hypertrophy was reached 18 to 24 months after the operation no patients required permanent supplementation. In two patients severe electrolyte disturbance required revision of the shunt.

Early in the shunt era the correction of transient electrolyte disturbance was a clinical problem. Since peroral magnesium was not available at that time, intravenous supplementation and hospitalisation was often necessary. With time the problem with electrolytes almost diminished.
Urine calculi (I)
We have, like many others, observed a considerable elevated risk for renal stones after JIB.\textsuperscript{49,56,69} Thirty-nine percent of the patients reported one or more attacks of suspected renal colic. It was only possible to confirm some of these attacks with a renogram. In eight patients, surgery was necessary to remove the stones, ESWL-treatment was used in one patient. Another patient had his shunt reversed mainly because of the problems with renal stones.

Urine calculus formation is believed to be due to an enteric hyperoxaluria. The increased amount of free fatty acids in the colonic contents is competitively bound to calcium leaving an increased proportion of free oxalate for intestinal absorption.\textsuperscript{120} This leads to excessive concentration in the urine, which together with a deficiency of magnesium, a potent inhibitor of crystal formation, results in a supersaturated urine with an increased risk for stone formation.

Some reports has claimed the JIB patients to be at risk of developing nefrocalcinos.\textsuperscript{36} No case of renal calcinosis was found in the present patient material. With the exception of one patient, normal levels of creatinine were found.

Hepatic disease

Liver failure (I,II)
Hepatic disease in the form of liver failure was found in five (5.5\%) of the present patients (I). The condition was diagnosed in these five patients 4 months, 1, 3, 5 and 14 years after JIB, respectively. JIB-related liver failure is characterised by hypoproteinemnia, oedema and fatigue. This is reported to be accompanied with jaundice, defect coagulation and even cerebral confusion in severe cases.\textsuperscript{21,49}

Early in this series one case of acute liver failure was presented with bleeding ulcer and jaundice. The surgeon, unaware of this complication of JIB, did not recognise the clinical situation and the patient died shortly after gastric surgery.
In the three other cases, of acute liver failure different antibiotic treatment (ampicillin, trimetoprimsulpha, metronidazole) were tried and all patients recovered within a week. The fifth patient had her shunt reversed due to liver failure before antibiotic treatment was evaluated.

Proposed causes of liver failure are abnormal bile salt metabolism, choline or protein deficiency or toxin released from bacterial overgrowth in the blind loop.\textsuperscript{46,59,98,131,136} The beneficial effect of protein infusion in patients with bypass-related liver disease support the protein deficiency theory.\textsuperscript{53}

As early as 1974 O"Leary showed that antibiotic treatment could prevent or reverse liver damage caused by JIB in dogs.\textsuperscript{86} Drenic in 1982 found that the early postoperative liver abnormalities in JIB patients could be reversed by treatment with metronidazole.\textsuperscript{37} These studies support the concept that growth of bacteria in the bypassed blind loop due to stopped luminal flow, promote translocation through the atrophic and inactivated mucosa.\textsuperscript{5,32,130} Bacterial toxins and subsequently formed immunocomplexes can not only induce liver disease but also polyarthritis since both conditions improve after antibiotic treatment.\textsuperscript{37,121}

Since the first reports of the usefulness of antibiotics were published, preferably metronidazole has been frequently used in the present series for different types of bacteria-related conditions such as arthritis, skin lesions or bypass enteritis. This might be one factor contributing to the absence of serious abnormalities in the late liver biopsies in the present series (II).

\textbf{Liver cirrhosis (II)}

The distribution of liver steatosis was not systematically investigated when these patients had their original operation. In the years to come several reports pointed out the risk of developing liver steatosis and eventually cirrhosis.\textsuperscript{52,55,73,116} Since no blood tests were known to predict or even reveal
early cirrhosis we felt obliged to investigate these patients in their long-term clinical follow up.

In 11 of the patients open wedge liver biopsies had already been performed during revisional surgery and operations for hernia, 1-14 years after the initial operation. Histologic evidence of fatty inflammation, fibrosis or even cirrhosis (group II-IV) were present in 54% of biopsies. Later, when a series of percutaneous liver biopsies were performed 14-20 years after the initial operation, the histologic changes were less pronounced (figure 6). Fatty fibrosis was found in 1/42 (3%) patients and cirrhosis was not found in any of these cases.

Figure 6. Diagram showing the histological findings in early (1-14 years) and late (14-20 years) liver biopsies. Classification according to Adler and Shaffner².

In five of the patients biopsies were taken both early and late. Four patients showed improvement in their late biopsies. The one patient with cirrhosis earlier had findings of only fatty liver in her late biopsy (figure 7).
Although there was no preoperative liver biopsies taken in the present series of patients it is reasonable to believe that the mild and insignificant histologic changes seen in the percutaneous series not only represent an absence of deterioration but may even indicate an improvement. The mean preoperative weight of 112 kg in this patient series implies a marked increased risk of liver steatosis or even cirrhosis already before operation. Fatty liver has been found in 80% of 1429 untreated morbidly obese patients.7 Liver cirrhosis has been found in 2.6-4% of patients prior to obesity surgery.7,8,4,116

It is known that the bypass procedure initially aggravate the liver steatosis in some patients.15,33,36,123 The lipid contents of the liver is dominated by triglycerides.123 Many authors consider this phenomena to be a progressive process eventually leading to fibrosis and cirrhosis.55,59 Others have found an
improvement after the first period of anabolism and weight loss with a subsequent decrease in hepatic lipid contents.\textsuperscript{15,33,123,135} This is in line with the present results. It is tempting to postulate that the initial increase is due to massive peripheral lipolysis with an increased overload of free fatty acids forcing the liver to synthesise and store triglycerides. The second period of decreasing hepatic lipid contents may be a the long-term effect of the nutritional balance and the markedly reduced body weight.

The postulated risk for liver cirrhosis was one of the major arguments for not including JIB in NIH consensus on obesity surgery.\textsuperscript{50} This opinion is based on several studies showing liver disease in JIB patients from referral centres including selected patients referred from other hospitals for reversals or conversions. The indications for these operations were not always stated but it is reasonable to believe that there is a selection bias with a high proportion of patients in poor metabolic condition and having liver disease.\textsuperscript{59,123,137} Studies on a complete unselected patient material and on the long-term consequences of JIB are scarce.

The present biopsy study cannot claim to have included the total patient material in this consecutive series. This was impossible to achieve since the patients for obvious reason had the freedom to deny participation due to fear of pain or bleeding complications or due to inconvenience if they lived a long distance away. Nevertheless 44 of 64 patients (65%) accepted participating as a part of their clinical follow up. The biopsy group and available patients in the non-biopsy group were compared with respect to age, body weight, weight after 14 years, and various metabolic parameters. The mean preoperative weight was 6% higher and the mean serum alkaline phosphatase 22% higher (but still in the normal range) in the non-biopsy group. Age, weight after 14 years, albumin, GGT, procollagen-III-peptide\textsuperscript{105} and triglycerides were not significantly different in the two groups. We, therefore, extrapolate the results to the total series and consider the selection bias to be minimal. Furthermore no clinical liver disease has been observed in the non-biopsy group and all are known to be alive.
Metabolic failure (I)

In a few patients in the present study the weight loss was too rapid and extensive often in combination with fatigue and electrolyte disturbances. The generally recommended treatment for this condition was to reverse the shunt completely.\textsuperscript{51,91,94,123} In the present series the surgeon instead performed a revision of the shunt on seven patients by adding 40-100 cm of the ileum to the intestinal continuity (figure 8) as advocated by Cegielsky and Nachlass.\textsuperscript{26,83} The final result was good in all but one patient, who gained too much weight. (table 3) The adapted method of reversals was probably the main reason for a low rate of reversal, 3.3\%, observed in this study.

![End to side bypass](image)

Figure 8. Revision of end-to side JIB, surgical procedure.

<table>
<thead>
<tr>
<th>Indication</th>
<th>Time after initial op. (months)</th>
<th>Length of ileal segment (cm)</th>
<th>BMI preop (kg/m(^2))</th>
<th>BMI at revision (kg/m(^2))</th>
<th>BMI at 15 years (kg/m(^2))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Electrolyte disturbance</td>
<td>20 (73*)</td>
<td>10 &gt; 100 &gt; 30</td>
<td>48</td>
<td>24 (36*)</td>
<td>29</td>
</tr>
<tr>
<td>Excessive weight loss</td>
<td>19 (36*)</td>
<td>10 &gt; 100 &gt; 20</td>
<td>35</td>
<td>14 (31*)</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>10 &gt; 100</td>
<td>32</td>
<td>17</td>
<td>26</td>
</tr>
<tr>
<td></td>
<td>22</td>
<td>10 &gt; 100</td>
<td>37</td>
<td>21</td>
<td>27</td>
</tr>
<tr>
<td></td>
<td>16</td>
<td>10 &gt; 60</td>
<td>37</td>
<td>18</td>
<td>27</td>
</tr>
<tr>
<td>Excessive weakness</td>
<td>3</td>
<td>10 &gt; 60</td>
<td>35</td>
<td>25</td>
<td>30</td>
</tr>
<tr>
<td>Electrolyte disturbance</td>
<td>26</td>
<td>10 &gt; 40</td>
<td>48</td>
<td>22</td>
<td>42</td>
</tr>
</tbody>
</table>

* = patients who have had two revisions, the second with a reshortening of the ileal segment.
Other types of revisions were a continent mucous fistula constructed of the blind loop in two patients and in five patients a conversion to bilio-intestinal bypass according to Eriksson. Indication for the fistulas were skin rash and fever expressing bacterial overgrowth in the blind loop. Metronidazole, glutamin, vitamins and minerals were installed into the fistulas and the symptoms subsided in both patients. Diarrhea and gas bloating, the reasons for converting to bilio-intestinal bypass, were persistent in three of the five patients.

Cancer risk (V)

Obesity and obesity surgery are both considered in the discussions of cancer aetiology. The obese state is per se associated with different types of neoplasm. Obesity is considered a risk factor for malignant diseases of, for example, breast, colon, rectum, prostate, endometrium, cervix, ovary, thyroid, kidney and gallbladder. The enteral and metabolic changes after JIB have also been postulated to increase cancer risk. On the other hand, the extent to which a weight reduction can decrease cancer risk is still unknown.

Relative risk (RR) for cancer, irrespective of localisation, was 2.0 (95%CI : 1.3-3.1) in the present study. The possible effect of weight reducing surgery was studied by deviding the observation time into two periods. Relative risk was 2.7 (95%CI : 1.4-5.3) before and within five years after the operation. The RR after five postoperative years was 1.6 (95%CI : 0.96-2.8). (table 4 and figure 9) We conclude that the risk for cancer was significantly increased within 5 years after the operation but not after that time. The impact of weight loss may be a contributing factor to the observed risk reduction.
<table>
<thead>
<tr>
<th></th>
<th>Case/Controls</th>
<th>Relative risk</th>
<th>95%CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colorectal cancer</td>
<td>4/6</td>
<td>1.6</td>
<td>0.4-6.0</td>
</tr>
<tr>
<td>Endometrial cancer</td>
<td>6/4</td>
<td>3.0</td>
<td>0.8-10.7</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>7/9</td>
<td>1.6</td>
<td>0.6-4.2</td>
</tr>
<tr>
<td>All malignant tumours</td>
<td>45/46</td>
<td>2.0</td>
<td>1.3-3.0</td>
</tr>
<tr>
<td>within 5 years postop.</td>
<td>20/15</td>
<td>2.7</td>
<td>1.4-5.3</td>
</tr>
<tr>
<td>after 5 years postop.</td>
<td>25/31</td>
<td>1.6</td>
<td>0.96-2.8</td>
</tr>
</tbody>
</table>

**Figure 9.** Diagram showing the distribution of all cancer cases, in relation to year for operation. The number of cases for the controls have been divided by two for relevant comparison.

**Colon cancer (IV,V)**

Obesity has been reported to be an independent risk factor for colon cancer. Relative risk between 1.2-2.4, depending on the degree of obesity, has been reported.\(^{65,78}\) There is also a correlation between energy intake and cancer risk.\(^{68}\) On the other hand caloric restriction can reduce rectal cell proliferation rate.\(^{12}\)
The increase in level of faecal bile acids in the colon after JIB may increase the risk for malignant transformation. Rectal hyperplasia and increased crypt cell production rate have been reported after JIB.\textsuperscript{9,19,20} Experimentally increased frequency of colon malignancies have been demonstrated in bypassed rats.\textsuperscript{20,79,100,113}

As a part of the clinical follow-up we conducted a colonoscopic study on 30 patients mean 13.9 years after JIB (IV). In each patient biopsies from six different locations in the colon were analysed with regard to histologic findings and DNA content in flow cytometry. All biopsies showed strictly diploid DNA content. The microscopic picture was dominated by hyperplasia with broadened mucosa and elongated crypts. One biopsy revealed a low-grade dysplasia in a structural lesion regarded as an initial tubular adenoma. There were no high-grade dysplasia or carcinoma.

To further investigate the risk of colorectal cancer after JIB the cancer incidence were studied on 830 patient from ten different hospitals in Sweden and compared to 1660 controls (V). The RR found in our study on 830 JIB-patients was 1.6 (95% CI;0.4-6.0), which does not indicate a significant increase in cancer risk. Since carcinogenesis can take a long time and the follow-up in the present study is relatively short, the possibility of increased cancer risk can not yet be ruled out. Longer follow up is needed to elucidate this issue.

**Endometrial cancer (V)**

The reported RR for endometrial cancer varies between 2.0 to 20.3\textsuperscript{3,10,42,64,66,78,114} One third of all cases of endometrial cancer in Europe have been estimated to be directly related to obesity\textsuperscript{64}. In the present study the RR for endometrial carcinoma was 3.0 (95 % ; 0.8-10.7). Our findings indicate that this cancer in the obese women not only has a higher incidence but also occurs earlier. Figure 10 demonstrates that 5 of 6 tumours were diagnosed before the operation or within five years of the operation. During the following 15 years of observation, only one case of endometrial cancer was diagnosed.
Although the number of cancer cases is very small, it is tempting to postulate that weight reduction decreases the risk for endometrial cancer. Others have also postulated this but there has been no conclusive evidence supporting this concept.

Figure 10. Diagram showing cases of endometrial cancer in relation to operation year.
GENERAL CONCLUSIONS

We have studied the long-term effects of the JIB over a 25 year period and found that:

- the weight reduction is extensive and permanent in the majority of patients
- the cardiovascular risk factors associated with obesity (diabetes, hyperlipidemia, hypofibrinolysis) are absent in more than 90% of the operated patients
- the risk for progressive liver disease is low
- the risk for colon cancer is not increased up to 20 years after JIB.
- the obesity-related overrisk for endometrial cancer tends to be reduced five years after JIB.
- JIB is associated with a number of adverse effects, which in most cases can be easily managed.
- metabolic failure or too rapid a weight loss after JIB could be managed by revision of the bypass.
- a readiness for revisions and the use of antibiotics (Metronidazole) are the main reasons for a low reversal rate.
- a mortality rate of less than 2% could be anticipated after JIB surgery.
The jejunoileal bypass surgery started as a great human metabolic experiment. The beneficial effects in terms of weight loss and reduced risk factors have been long-standing. Since most adverse effects could be managed the operation deserves a reconsideration as an alternative for selected obese patients.

**Subjects for future studies**

- **Metabolic syndrome:** The JIB reduce insulin resistance and other risk factors before weight reduction is achieved. How is that? What are the partial bypass effects on the fibrinolytic system? Which intestinal hormones are involved?

- **Cancer risk:** Is it possible to reduce obesity-related cancer risk? Is the observed increased cancer risk in the present study related to obesity or the bypass procedure. Prolonged and extended epidemiological studies will be needed.
REFERENCES


59. Kaminski DL, Herrman VM, Martin S. Late effects of jejunoileal bypass operations on hepatic inflammation, fibrosis and lipid content. Hepatogastroenterol 1985;32:159-162.


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