

„IN SEARCH OF THE OPTIMAL RECONSTRUCTION METHOD
AFTER TOTAL GASTRECTOMY”

Ph. D. Thesis

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I. INTRODUCTION

1. Total Gastrectomy

1.1. Physiological Functions of the Stomach Lost by Total Gastrectomy

The stomach as a dilated portion of the upper gastrointestinal tract, functions as a reservoir. It transports food from the oesophagus to the small bowel, while mechanically breaking food down and partially digesting it by hydrochloric acid and pepsin.

The lower oesophageal sphincter protects the oesophagus from gastric and duodenal juices. When resected – in case of a total gastrectomy - this protection is lost. Though recently there are tendencies toward preservation of the lower oesophageal sphincter if it is oncologically possible (1).

The fundic region can hold large amounts of food, regulated by vagal reflexes (accommodation and receptive relaxation). Loss of this function results in reduced reservoir capacity, an early fullness feeling during meals, which is often described as epigastric discomfort (2).

Tonic contractions of the body and antrum grounds and propels the food towards the duodenum and delivers it in small boluses via the pyloric sphincter. The pylorus controls the emptying of the stomach and prevents duodeno-gastric reflux. The motility of the stomach is paced from a distal region at the greater curvature, where smooth muscle cells have the highest intrinsic activity for contraction (2). This grounding of food can partly be replaced by thorough chewing or eating mashed food, however if food remains improperly minced, the digestive process will certainly be less than perfect.

The loss of hydrochloric acid production does not necessarily result in any obvious disturbances. Some claim that hydrochloric acid keeps a low number of micro-organisms in the upper gastrointestinal tract, and the lack of it results in bacterial overgrowth, consumption of vitamins and micronutrients (3). There are studies though, which proved

no difference in bacterial culture of jejunal aspirates of patients after total gastrectomy, compared to healthy controls (4).

The loss of parietal cell mass on the other hand certainly leads to a complete lack of intrinsic factor, which – when left unattended – leads to pernicious anaemia.

Gastrointestinal hormones play a major role in the regulation of gastrointestinal secretions and motility. Removal of the stomach is a rather rude intervention in this sense, which disarranges the harmony in the production of gastrointestinal hormones. The resulted state of disorder is often referred to as pancreatico-cibal asynchrony (5).

Gastrin has its most important role in acid secretion. Its production is increased by vagal impulses as well as by protein degradation products in the stomach, the latter raises gastrin level exponentially with a positive feed back (6). Acid appearing in the antrum stops production of gastrin, thus regulating acid release via a negative feed back. Gastrin level is markedly reduced in gastrectomised patients not only because most of it is produced in the stomach, but also because the feed back regulation is lost (7).

Cholecystokinin stimulates pancreatic secretion, contracts the gall bladder and slows gastric emptying. The arrival of a bolus to the duodenum increases cholecystokinin output, which in turn increases pancreatic juice production as well as relaxes the fundic region of the stomach and contracts the pylorus (8). Regarding the stimulation of digestive juice production, the nutrients braking down to smaller elements increase cholecystokinin production further, switching on a positive feed back regulation (6). In relation to gastric emptying a negative feed back works. In the lack of stomach, cholecystokinin, however high its level raises, cannot stop the food flowing uncontrolled to the duodenal bulb. Not to mention if duodenum is excluded, and endocrine cells in the duodenum and the Y limb are informed only via neural and hormonal pathways about the fact, that digestion is supposed to be going on.

Gallstones are detected at a higher frequency after total gastrectomy (9). And a considerable percentage of these are symptom

free. The raised and fairly constant level of cholecystokinin, as well as truncal vagotomy leading to relaxation of the gallbladder are the most important factors involved in the formation of postgastrectomy gallstones (10).

The perception of hunger changes significantly after gastrectomy. Some patients feel constant hunger, others never experience the same motivation for eating as before surgery. The blood levels of nutrients and hormones, which have a major role in regulation of eating behaviour, fluctuate much more in the lack of the stomach. The postprandial tension of the gastric fundus via a neural pathway and ghrelin, produced in the stomach via humoral ways, signals to the brainstem to reach the feeling of satiety (11). These are lost in the lack of stomach. Cholecystokinin was repeatedly shown to have an appetite-suppressing effect (12). Its raised levels after gastrectomy might add to the reduced food intake.

Glucose homeostasis suffers a special change after removal of the stomach (13). The lack of the stomach results in a shockingly fast absorption of glucose from the small bowel to blood stream resulting in hyperglycaemia. A strong response from the endocrine pancreas yields hyperinsulinaemia. This is magnified by enteroglucagon, which is produced at a higher level because of the excess of sugar in gut lumen (14). The result can be a late postprandial hypoglycaemia, which is the late dumping syndrome itself.

1.2. Indications for Total Gastrectomy

Total removal of the stomach is a demanding operation for the surgeon as well as for the patient. There is a considerable operative morbidity ranging between 15-30% and operative mortality between 3-10%. The operative mortality for 345 patients between 1993 and 2002 at the Department of Surgery University of Pécs was 6,9 %.(15). Considering the risks and benefits, it is rare to perform total gastrectomy on a patient without a good reason (occasional prophylactic gastrectomies). The overwhelming majority of these patients are operated on for gastric cancer. Some total gastrectomies are performed

for bleeding ulcers with or without Zollinger-Ellison syndrome, somewhat more are carried out for nonepithelial gastric tumors, such as GISTs or lymphomas. As a consequence of the above, symptoms seen after total gastrectomy are results of not only the lack of the stomach, but also, to some extent, symptoms of the basic disease.

1.3. Method of Total Gastrectomy

Although the laparoscopic technique for total gastrectomy has been elaborated (16), total gastrectomy is routinely performed as an open operation. The access to the stomach is readily available via a midline incision which is supplemented by a transverse incision if necessary for obese patients or more extensive surgery. The most comfortable access to the cardiac region is via a left sided thoracotomy. Some authors feel it inferior to laparotomy with splitting up the diaphragm, for its higher morbidity (17). After exploration of the abdominal organs decision for radical (R0) resection can be made depending on the extent of the disease. The greater omentum is dissected down the transverse colon. The dissection is forwarded onto the transverse mesocolon, to remove the covering peritoneal layer, thus the posterior wall of the lesser sac. This so called bursectomy reduces the chance of peritoneal seeding. Towards the left, the left gastroepiploic artery and the gastro-splenic ligament are divided or in cases of upper third tumour or direct invasion the spleen is removed. The oesophagus is freed in the oesophageal hiatus, the gastro-hepatic ligament is divided closer to the liver. Towards the right the right gastroepiploic vessels, the right gastric artery and the duodenum are divided, the duodenal stump is permanently closed with a linear stapler or only temporarily with clamps, depending on the reconstruction type chosen. D2 lymphadenectomy is performed if the indication is gastric cancer. Lymph node dissection starts at the gastroduodenal artery and a systematic peeling off of all lymphatic tissue is carried out along the primary hepatic artery, common bile duct and portal vein. Dissection follows the upper border of the pancreas by clearing the common hepatic and the splenic artery, dividing the coronary vein and left gastric

artery at its origin from the celiac trunk. After dividing few remaining tissues along the diaphragmatic crura between the celiac trunk and the oesophageal hiatus, the stomach is removed. The reconstruction of the continuity of the gastrointestinal tract can be restored following various methods (see chapter 2.)

1.4. Physiological Consequences of Total Gastrectomy

The long term consequences of total gastrectomy are weight loss, malabsorption, anaemia, disturbed gastrointestinal motility, referred to as dumping (see 1.5.) and alkaline reflux (see 1.5.).

The average weight loss after total removal of the stomach is around 15 % of the original healthy body weight (14). The reason for weight loss is partly the malabsorption itself, but there is also a reduced initiative for food intake, the background of which needs further clarification.

Malabsorption of nutrients has also a complex aetiology. The lack of the stomach results in a faster transit of food, a disturbed gastrointestinal hormone production, a reduced stimulation to the pancreas, what is most pronounced if the reconstruction excludes the duodenum from the food passage. Exocrin pancreatic insufficiency is secondary to pancreato-cibal asynchrony i.e. disharmony in food passage and digestive juice production because of a disturbed order and magnitude of gastrointestinal hormone secretion (6). There is also a primary insufficiency of the pancreas proven by secretin-coerulein test, for which the reason is supposed to be the nerve damage caused by peripancreatic dissection during total gastrectomy (8,18).

Anaemia after total gastrectomy originates from B12-vitamin and iron deficiency. B12-vitamin deficiency directly comes from the complete abolishment of intrinsic factor producing gastric mucosa. Iron deficiency is secondary to a malabsorption of iron in the duodenum either because of accelerated passage through the duodenum, or in cases of reconstructions excluding the duodenal route because of no passage through the duodenum.

1.5. Postgastrectomy Syndromes

Long term consequences of gastrectomy are commonly summarised as postgastrectomy syndromes (3) (table 1). Only syndromes after total gastrectomy and not ones after partial gastric resection are encountered here, especially for some of the latter (such as afferent and efferent loop syndromes) are rather results of an improper surgical technique, than consequences of loss of the stomach.

Table 1: Postgastrectomy syndromes

Postgastrectomy syndromes:
Reduced reservoir capacity
Dumping
- Early
- Late
Alkaline reflux
Roux stasis

Reduced reservoir capacity is a direct consequence of the fact, that instead of the large, strong-walled, dilated sack of stomach, a finer, narrower organ, the small bowel is sutured to the end of the oesophagus to receive the arriving boluses of food. Guts are sensitive only to tension of their wall. The stomach not only being larger, but also helped by the special vagal reflex of receptive relaxation in the fundic region can accommodate very well to the size of the meal, thus avoid the development of such a tension. A normal size meal cannot fit into the proximal end of the Roux-limb, not even into a pouch of small bowel duplicate, without considerable tension, experienced by the patient as considerable epigastric discomfort. Patients are suggested to ingest small-volume meals more frequently. The receiving small bowel portion dilates with time up to about 400 millilitres (19), which allows larger but still not a normal size of meal to be eaten.

Dumping was described by Mix in 1922 as a rapid emptying of gastric content on radiography in patients with this condition (20). It is the most frequently encountered but less well defined syndrome after gastrectomy. Two types can be differentiated, early and late dumping.

Early dumping is comprised of vasomotor and / or gastrointestinal symptoms starting 10-30 minutes postprandially. The reason for it is the sudden appearance of a large volume of high osmolarity (high carbohydrate) liquid in the small bowel, resulting in a fluid shift from the intravascular space to the bowel lumen. The pathophysiological background is supported by experimental evidences of a reduction in packed cell volume, increase in intravascular fluid osmolarity parallel to a fall in blood pressure and elevation in pulse rate in patients experiencing dumping (21). Several gastrointestinal hormones were examined and found to be released during dumping (22, 23, 24). Somatostatin can alleviate or prevent symptoms (21). Vasomotor symptoms are weakness, dizziness, flushing, sweating or palpitation. Gastrointestinal symptoms can accompany vasomotor symptoms or can be present alone, such as fullness, cramps, nausea and sudden diarrhoea.

Late dumping is a better defined pathological category, with vasomotor symptoms only, occurring 2-4 hours after a meal. The background is the release of enteroglucagon in response to high carbohydrate load in the small bowel, which brings about excessive amount of insulin release, resulting in a drop of blood sugar. The presenting symptoms are similar to that of hypoglycaemia (25).

Resection of the cardia results in free reflux of bowel content into the oesophagus after total gastrectomy. If this content is irritating for the oesophageal mucosa the patient will experience heartburn, maybe nausea and vomiting and in the long term oesophagitis, Barrett metaplasia or even Barrett cancer develops. The noxious content is bile. It is the surgeon's most important task while choosing the reconstruction type after total gastrectomy to avoid any possibility for bilious reflux to the oesophagus. This is why Ω -loop reconstruction is unacceptable and in cases of Roux-en-Y or Longmire reconstructions the jejunal limb has to be long enough (40-50 cm) to prevent alkaline reflux.

Roux stasis syndrome occurs in almost one third of patients, undergone total gastrectomy and simple Roux-en-Y reconstruction (3).

Symptoms are that of upper gastrointestinal stasis, i.e. early fullness during meal, epigastric discomfort, nausea and regurgitation. The symptoms are the manifestation of a motility disorder thought to develop because the Roux jejunal limb is divided from the duodenal pacemaker (3). Others experienced a positive correlation between the length of the Roux limb and the occurrence of the symptoms (26). Whilst a long limb is preferred as a protection against reflux, a shorter limb reduces the incidence of Roux stasis syndrome. In Roux limbs shorter than 40 cm the symptoms hardly can develop (3). This observation may be explained by the jejunum's ability to pace the contractions of a certain length of small bowel only.

2. Techniques of Reconstruction after Total Gastrectomy

2.1. Types of Reconstructions

The first total gastrectomy was attempted by Phineas Conner of Cincinnati in 1884 (27). The first successful one was performed by C. Schlatter of Switzerland in 1897 (28). Since then surgeons tried more than sixty different reconstruction types to re-establish gastrointestinal continuity after removal of the stomach. Zoltán Szabolcs in his excellent monography about gastric cancer published in 1966 had collected 58 different reconstruction types after total gastrectomy as represented in figure 1. The high number indicates that there is no optimal solution found to this problem.

Figure 1: Different methods to replace the removed stomach or to reconstruct gastrointestinal continuity after total gastrectomy or fundectomy. Szabolcs Zoltán: A gyomorrák. Akadémiai Kiadó, Budapest 1966.

To re-establish continuity between the oesophagus and the small bowel, the most straightforward ways are direct oesophago-duodenostomy, as done by Conner or Ω -loop oesophago-jejunostomy

(figure 2a,b) as performed by Schlatter. The oesophago-duodenostomy is prone to be under tension, which prevents anastomotic healing, though with a thorough mobilisation of the duodenum and pancreatic head the anastomosis can be performed in almost all cases (Nakayama 1955) (29). Nevertheless oesophago-duodenostomy and omega-loop oesophago-jejunostomy both results in debilitating biliary reflux, thus they are not recommended in surgical practice any longer.

In the historical evolution of omega-loop oesophago-jejunostomy, to prevent reflux and postprandial symptoms, an additional jejuno-jejunal anastomosis – a shorter (Hoffmann 1922) (30) or a longer one (Steinberg 1950) (31) - was introduced between the afferent and efferent limbs of the Ω -loop, with still no satisfactory results regarding reflux oesophagitis (figure 2c,d). Others, trying to reconstruct the original anatomical situation, suggested the interposition of a reservoir at the site of the stomach, between the oesophagus and the duodenum. Interposition of a segment of jejunum (Seo 1942, Longmire 1952) (32,3), ileocolon (Hunnicut 1952) (33) and transverse colon (State 1951) (34) was performed (figure 2 e,f,g).

The today gold-standard reconstruction, the Roux-en-Y oesophago-jejunostomy is based on Cezar Roux's concept applied after partial gastric resection in 1892 (35). It was T. G. Orr who first applied this technique after total gastrectomy in 1947 (figure 2h) (36). With this reconstruction alkaline reflux can be avoided in almost all cases.

The above, basic reconstruction types provide a route for passage between the oesophagus and the small bowel while more or less preventing backward passage, i.e. reflux, but they fail to replace any other functions of the stomach.

To replace reservoir function of the stomach, gastric substitutes, the so called pouches have been introduced.

C. J. Hunt in 1952 published his technique of a double plication of jejunum at the proximal end of the Roux limb and creation of a reservoir by suturing a side-to-side jejuno-jejunostomy (figure 2i) (37). Rodino in 1952 and Lawrence in 1962 published only slightly different methods (38, 39). Their technique, the Hunt-Lawrence-Rodino pouch or

J pouch – as called by Herfarth in a review in 1988 – is the most well-known pouch type worldwide (40). Other techniques apply triple plication of the jejunum (Hays and Clark in 1960) (41), interposition of ileocolon (Hunnicut 1952) (33), transverse colon (State 1951, Gerwig 1952) (34, 42), or a long double plication of jejunum with partial length of side-to-side anastomosis (Lygidakis 1981, Konjovic 1997) (43,44). To prevent oesophagitis antireflux valve can be created from jejunum (Siewert and Peiper 1973) (45).

It was Imre's idea first to place the reservoir under the mesocolon, instead of at the site of the removed stomach (1975) (46). In his method there is a second anastomosis performed between the Roux limb and the Y limb, to involve a larger portion of the otherwise excluded Y limb in the passage, thus in the absorptive process (figure 2j). The opposite direction of peristalsis in the two limbs between the two anastomoses supports a mixing of food at this level of the gastrointestinal tract. Imre's circuit pouch theoretically reduces food flow, improves absorption, but does not increase reservoir capacity. Aboral pouch – developed from Imre's circuit pouch by our research group – theoretically retains the above advantages and adds an increased capacity because of the long side-to-side anastomosis created between the limbs (figure 2k).

Figure 2: Reconstruction types

2.2. Importance of Pouch Construction

Regarding the question, whether it is advantageous to create a pouch after total gastrectomy, there are believers and non-believers, both are having considerable arguments on their sides. Pouch supporters say a pouch is a widened portion of the gastrointestinal tract, where - following physical rules – the passage slows down. This may prevent dumping and gives more time for digestion and absorption. And of course the widened gut provides a larger reservoir capacity, which allows the patients to take larger meals at once.

On the other hand, non-believers say that, to cut through the small bowel wall longitudinally, disturbs the peristaltic motility of the limb, the result of which is unpredictable, can be stasis as well as sudden run of food through the irregularly contracting portion. Others claim, that in the long term side-to-side anastomoses slowly forms into end-to-side ones and no long reservoir remains.

To tell which is true, it is impossible as well as outdated without using the magic tool of evidence based medicine.

About the creation of a pouch after total gastrectomy, fifteen prospective randomised trials have been published by now (table 2). Two excellent reviews also has been published in which the feasibility of a formal meta-analysis has been examined, however endpoints to describe treatment results varied so much across trials, as did the definition and presentation of results and the length of follow-up, that it precluded any formal statistical meta-analysis of all trials (47, 48)

Table 2: Randomised trials to examine importance of pouch construction

Author	Year	Patient number	Reconstruction types	Follow-up (months)	Reservoir function	Transit	Body weight	Quality of Life	Summary
Troidl (59)	1987	38	ΩOJ vs RYP	12	Better for pouch	-	Better for pouch	Better for pouch	Pouch better, but ΩOJ is anyway
Schmitz (50)	1994	39	JIP vs JIPP	6	Better for pouch	Less vomit	NS	NS	NS
Nakane (51)	1995	30	RYP vs RY (vs JIPP)	24	Better for pouch	Better for pouch	Better for pouch	-	Pouch better
Liedman (19)	1996	77	RYP vs RY	12	NS	-	Better for pouch	-	Pouch better
Bozetti (52)	1996	48	RYP vs RY	24	-	Better for pouch	-	Better for pouch	Pouch better
Schwarz (53)	1996	60	RYP vs RY (vs JIPP)	6	-	-	NS	NS	NS, though GI hormone better for
Tanaka (54)	1997	21	RYP 15 cm vs RYP 20 cm	12	-	-	NS	-	NS
livonen (55)	1999	51	RYP vs RY	60	-	-	-	NS	NS
Büchin (56)	1999	20	JIP vs JIPP		-	-	NS	-	NS
Hoksch (57)	2000	49	JIP vs JIPP 7 cm vs JIPP 15 cm	12	-	-	NS	NS	NS
Gioffre-Florio (58)	2000	41	RYP vs RYPP	12	-	-	Better for RYPP	Better for RYPP	Double pouch better than single
Fujiwara (59)	2000	40	RYP vs RY DTP	12	NS	NS	NS	-	NS
Horváth (60)	2001	46	RY vs AP	12	-	NS	NS	Better for AP	Better for pouch
Kono (61)	2003	47	RYP vs RY DTP	48	-	-	NS	Better for RYDTP	Better for pouch
Mochiki (62)	2004	26	JIP vs JIPP	44	Better for JIP	Better for JIP	NS	-	Worse for pouch

ΩOJ: Ω-loop oesophago-jejunostomy RY: Roux-en-Y, RYP: Roux-en-Y plus pouch (the Hunt pouch), JIP: jejunum interposition (Longmire), JIPP: jejunum interposition plus pouch, RYPP: Roux-en-Y with double pouch, RYDTP: Roux-en-Y with double tract and pouch, AP: aboral pouch, NS: not significant

In the fifteen prospective randomised trials listed in table 2 altogether 633 patients were involved, which seems a high enough number to answer a simple question, whether to create or not to create a pouch. Unfortunately not only two, but eight different reconstruction types are involved. And even a group with the same reconstruction type will not certainly mean same procedures, as for example Roux-en-Y is performed from 30 to 50 centimetres long Roux limbs. Pouch sizes are different also. Measurement of reservoir capacity, motility and quality of life were performed by different means.

Nevertheless it is important to note that, out of fifteen studies seven concluded that to construct a pouch is better, seven that it is not significantly better and one that it is actually worse for the patient. Quality of life was determined in nine studies, of which five found a better quality of life if the reconstruction involved pouch construction after total gastrectomy, while in four no significant difference was revealed in favour of pouch construction. Body weight was measured in all but two trials. Pouch did not result in significant advantage in keeping weight in nine studies, while did indeed in four. Reservoir capacity and motility were tested in less than half of the trials with highly variable results.

2.3. Importance of Duodenal Passage

Common sense suggests that preservation of the duodenal route is important. The food passing through the duodenum brings about production of gastrointestinal hormones such as cholecystikinin, secretin, GIP, motilin, enteroglucagon etc. Though one of these hormones' target organs is missing after removal of the stomach, the duodenum, the biliary tract and most importantly the pancreas are there to be stimulated to improve digestion. Besides, the duodenum is the site of absorption for iron and calcium. Symptoms of iron and calcium deficiency are frequently encountered in patients after total gastrectomy.

Notwithstanding most studies in the literature could not reveal any significant advantage in favour of preserving the duodenal passage.

Regarding evidences in the preservation of the duodenal route the same applies at a higher degree like for pouch construction. There were even less prospective, randomised trials and the low number of cases, the differences in endpoints, definition of variables and follow-up precludes drawing a straightforward conclusion in the form of meta-analysis. Nevertheless it is worthwhile to go through the results of the six prospective randomised trials available from the literature (table 3).

Table 3: Randomised trials to examine importance of duodenal passage preservation

Author	Year	Patient number	Reconstruction types	Follow-up	Reservoir function	Transit	Body weight	Quality of Life	Summary
Basso (63)	1985	22	RY vs JIP		-	-	NS	-	NS
Raab (64)	1987	27	RY vs JIP	12	-	-	NS	NS	NS
Fuchs (65)	1995	106	RYP vs JIPP	36	NS	NS	NS	NS	NS
Nakane (51)	1995	30	RYP vs JIPP (vs RY)	24	Better for DP	Better for DP	Worse for DP	-	NS
Schwarz (53)	1996	60	RYP vs JIPP (vs RY)	6	-	-	NS	Better for JIPP	Duodenal passage better
Nakane (66)	2001	30	RYP vs JIPP	24	Better for RYP	-	NS	-	NS

RY: Roux-en-Y, RYP: Roux-en-Y plus pouch (the Hunt pouch), JIP: jejunum interposition (Longmire), JIPP: jejunum interposition plus pouch, NS: not significant

In these six trials comparing reconstructions with or without preservation of the duodenal passage altogether 275 patients were involved with four different reconstruction types. Five out of six studies failed to show a significant difference between the tested groups. In Schwarz et al's study duodenal preservation resulted in significant weight gain and a better quality of life as well a more physiologic

glucose homeostasis was observed with lower sugar and higher insulin levels.

In Schwarz and Beger's review in 1998, when only seven prospective, randomised trials were available, they concluded, that curatively operated patients with a good long-term life expectancy might benefit from a pouch reconstruction with maintenance of the duodenal passage, however clinical benefit is manifested not earlier than 6 months (47). For patients with poorer prognosis a Hunt pouch (Roux-en-Y plus pouch) was suggested and simple Roux-en-Y only for high risk patients, who cannot tolerate long surgery.

In 2004 Lehnert and Buhl revisited the topic and reviewed nineteen trials (48). As mentioned above, the heterogeneity of the trials precluded a formal meta-analysis. They concluded that there was little evidence to support preservation of duodenal transit. Regarding the construction of a pouch, it was associated with better food intake and weight development, at least in the early period after operation. With prolonged follow-up the advantages of pouch construction seemed fewer, but a favourable perception of quality of life persisted. They did suggest construction of a gastric substitute after total gastrectomy, and because it seemed especially advantageous in the early postoperative period, it was suggested for patients undergoing palliative resection too.

The suggestions of the two expert reviews are quite similar, the reasoning behind it, is rather opposite. And if one looks through table 2 and 3 one must feel that the question of optimal reconstruction after total gastrectomy is not yet answered.

II. THE OPTIMAL RECONSTRUCTION METHOD AFTER TOTAL GASTRECTOMY

The ideal reconstruction method replaces all lost functions of the stomach, ie. provides a large enough reservoir, which can accommodate to the size of the meal, prevents reflux, as well as dumping, ensures well grunted equal sized boluses of chyme entering the duodenum and responds properly to the changing levels of gastrointestinal hormones and neural information. Science of surgery is not any near to reach this idol.

In the present state of research the importance of reservoir construction and duodenal passage preservation are under evaluation.

1. Objectives of the trials in search of the optimal reconstruction type after total gastrectomy

1.1. General objectives

- 1) Introduction of a Roux-en-Y based, theoretically new reservoir construction – the Aboral Pouch (AP)
- 2) Comparing Aboral Pouch (AP) to the gold-standard Roux-en-Y (RY) reconstruction in a prospective, randomised manner (Trial-I)
- 3) Introduction of another new type of reconstruction where Aboral Pouch is combined with the preservation of the duodenal passage: the Aboral Pouch with Preserved Duodenal Passage reconstruction (APwPDP)
- 4) Comparing Aboral Pouch (AP) to Aboral Pouch with Preserved Duodenal Passage (APwPDP) and to control Roux-en-Y (RY) to examine the importance of duodenal passage preservation

(Trial-II)

- 5) Comparing Aboral Pouch with Preserved Duodenal Passage (APwPDP) to the more widely used Oral or Hunt-Lawrence-Rodino pouch with preserved duodenal passage (OPwPDP) in a prospective randomised way to examine the importance of the site of the pouch (Trial-III)
- 6) Examining gastrointestinal hormone production after a test meal in different reconstruction types (Trial-IV)

1.2. Endpoints

Primary endpoints or outcome measures of each trials except trial-IV were body weight, or expressed better as change in body mass index (in percentage of early postoperative body mass index), and quality of life measured by the gastrointestinal quality on life index (GIQLI) (in points).

Secondary outcome measures are the measured laboratory parameters (serum total protein, albumin, triglyceride, cholesterol, hemoglobine, iron, transferrin saturation, transferrine, immunoglobulin-A, immunoglobulin-G, immunoglobulin-M, Odonera's prognostic nutritional index (OPNI)), motility measures (scintigraphic small bowel passage (SSBP)) and measures of absorption (lipid absorption, carbohydrate absorption).

1.3. Eligibility criteria, randomisation

All patients with a disease necessitating total gastrectomy were investigated for eligibility to enter the trial. Patients younger than 80 years old, who have had no historical data of previous bowel resection and the kidney and liver function tests had shown normal results, in whom R0 resection could be performed, were considered eligible. During the operation after evaluation of the feasibility of all reconstruction methods and clearance for technical resectability randomisation was performed via the envelope selection method.

2. Patients and Methods

2.1. Patients

2.1.1. Trial-I

Patient accrual for Trial-I took place between 1997 and 2000. Forty-six patients entered the trial, 24 to the Aboral Pouch (AP) group and 22 to the control Roux-en-Y (RY) group (Reconstructions are described in details in section 2.2.). Patients' characteristics are represented in table 4. There were no significant difference between the two groups according to age, histology of the stomach disease necessitating total gastrectomy, stage, duration of the operation and hospital stay. The rate of postoperative complications were neither different. During the operation splenectomy was necessary in 5 pouch patient and 3 controls, reoperation because of bleeding had to be done in one control patient. No anastomotic insufficiency occurred in this population, one intraabdominal abscess developed in a pouch patient, one postoperative pulmonary embolism was observed in each group, none of them fatal, and two pouch patients developed left sided hydrothorax.

Table 4: Patients' characteristics in Trial-I

Trial-I	Aboral Pouch	Roux-en-Y	
n:	24	22	
Age	58,0	63,2	NS
Gender: Male/female	12/12	12/10	NS
Hystology: ACC/other	21/3	21/1	NS
Stage for ACC: Stage I/II/III	0/4/17	2/4/15	NS
Operative time	178 ± 9 min	169 ± 14 min	NS
Hospital stay	15,2 ± 2,2 days	15,4 ± 3,3 days	NS

ACC: adenocarcinoma, NS: not significantly different

2.1.2. Trial-II

From year 2000 a third arm was added to the randomisation process and Trial-II - to compare Aboral Pouch (AP), Aboral Pouch with Preserved Duodenal Passage (APwPDP) and Roux-en-Y (RY) reconstructions - has been started on. Patient accrual was closed in 2002. Patients of Trial-I were also included and followed. The final number of patients entered the trial was 98, thirty-five patients in the Aboral Pouch (AP) arm, twenty-five patients in the Aboral Pouch with Preserved Duodenal Passage (APwPDP) arm and thirty-eight patients in the control Roux-en-Y (RY) arm (table 5). At 6 months follow-up all patients, at 12 months 66 patients (67,3%), at 24 months 55 patients (56,1%) and for long term review 35 patients (35,7%) were available for study examinations. Reasons for withdrawal were mainly recurrent adenocarcinoma. Unavailability and unwilling to attend were observed mainly at the long term follow-up. During the 24 months of the study 14 patients were lost to follow-up in AP group, 10 in APwPDP and 19 in RY. Reasons for drop-out are summarized in table 6.

Patients' characteristics for Trial-II are represented in table 5. The groups did not differ significantly according to age, distribution of gender, histological type and stage of disease. Non-adenocarcinoma cases were two lymphomas and two gastrointestinal stromal tumors in AP group, one lymphoma in APwPDP group and one lymphoma and one fibrosarcoma in RY group. Mortality and morbidity did not differ significantly comparing the three groups. One patient died in the pouch group after discharge from hospital within one months postoperatively and as no autopsy was performed, the reason is unsure, probably embolism. No pouch or duodenal anastomosis related postoperative morbidity have been experienced. One anastomotic insufficiency at the esophago-jejunosomy occurred – in a patient in APwPDP group - which was successfully managed by conservative treatment. Pouch construction added approximately 10-15 minutes, duodenal anastomosis a further 10 minutes to the operating time. The hospital stay was independent of the reconstruction method chosen.

Table 5: Patients' characteristics in Trial-II

Trial-II	AP	APwPDP	RY	
n:	35	25	38	
Age	58,26	58,79	62,73	NS
Gender: Male/female	22/13	14/11	26/12	NS
Hystology: ACC/other	31/4	24/1	36/2	NS
Stage for ACC: Stage I/II/III	6/4/21	3/5/16	4/6/26	NS
Operative time	179 ± 24	192 ± 31	165 ± 16	NS
Hospital stay	15,5 ± 3,3	15,7 ± 5,0	14,9 ± 3,4	NS

ACC: adenocarcinoma, NS: not significantly different

Table 6: Reasons for dropout during 24 months follow-up of Trial-II

Trial-II	AP	APwPDP	RY
Peritoneal carcinosis	5	3	3
Liver metastases	2	1	3
Pulmonary metastases	-	1	-
Suprarenal metastasis	-	1	-
Retroperitoneal recurrence	3	1	7
Mediastinal recurrence	-	-	1
Krukenberg's tumour	1	-	-
New colorectal cancer	-	1	-
Requested to withdraw	1	-	1
Not known	2	2	4
All	14	10	19

2.1.3. Trial-III

The accrual period for Trial-III was between 2002 and 2004. Patients were randomised either to undergo Aboral Pouch with Preserved Duodenal Passage (APwPDP) or Oral Pouch with Preserved Duodenal Passage (OPwPDP) reconstruction after total gastrectomy. Fourteen patients entered APwPDP group, fourteen the OPwPDP group. One patient from OPwPDP group withdrew her consent before the basic, two weeks postoperative measurements, so she was excluded from the study. Thus 14 APwPDP and 13 OPwPDP patients' data were analysed. Patients' characteristics are summarised in table 7. No difference has been revealed between the two groups according to age, sex, histology and stage of the disease, neither in operative time

and hospital stay. No mortality has been observed in this patient population and neither any reconstruction related morbidity.

Table 7: Patients' characteristics in Trial-III

Trial-III	APwPDP	OPwPDP	
n:	14	13	
Age	57,75	61,18	NS
Gender: male/female	5/9	6/7	NS
Hystology: ACC/lymphoma	13/1	12/1	NS
Stage for ACC: stage I/II/III	4/6/4	5/5/3	NS
Operative time	188 ± 8 min	189 ± 15 min	NS
Hospital stay	14,2 ± 3,2 days	15,0 ± 3,4 days	NS

ACC: adenocarcinoma, NS: not significantly different

2.2. Operative Methods

2.2.1. Aboral Pouch

After total gastrectomy and D2 lymphadenectomy, a Roux limb was prepared. The end of both the oral jejunal limb and the Roux limb were closed with a stapling device. The oesophagojejunostomy was performed end to side manually with one layer running sutures. To create the aboral pouch an antiperistaltic side to side jejuno-jejunosomy, measuring 15 cm in length was constructed manually, with one layer running sutures, between the Roux limb and the end of the Y limb, under the mesocolon, 50 cm distal to the oesophagojejunostomy (figure 3) (67)

Figure 3: Aboral Pouch reconstruction

2.2.2. Aboral Pouch with Preserved Duodenal Passage

After total gastrectomy and D2 lymphadenectomy a Roux limb is prepared from the first jejunal loop. Both ends of the loop are closed. The oesophago-jejunosomy is constructed between the esophagus and the Roux limb, end to side with one layer running suture. Approximately 50 cm far from the oesophago-jejunosomy a side-to-end jejuno-duodenostomy is created between the Roux limb and the duodenal stump with one layer running suture. Right below this second

anastomosis the Roux limb is closed with a linear stapler to provide a unidirectional food passage through the duodenum. An aboral pouch is constructed as a side-to-side anastomosis between the Roux limb some centimetres under the stapled segment and the aboral end of the Y limb, measuring 15 centimetres in length (68, 69).

There was a slight modification of the jejuno-duodenal anastomosis and the closure distal to it, because, in the meantime a suggestion has been published that staplelines, like the one applied under the duodeno-jejunostomy might open up (70). If this happens, the food has two routes to choose, either goes through the duodenum and enters the pouch from the Y limb after the ligament of Treitz, or passes through the opened up stapled part of the Roux limb and enters the pouch without passing through the duodenum. This would make APwPDP reconstruction one of the double tract reconstructions (59). To prevent this we modified the technique and cut the bowel where it was only stapled before. The mesentery of the Roux limb was left intact. The oral end was sutured to the duodenum in an end to end manner, the aboral end was closed (figure 4).

Figure 4: Aboral Pouch with Preserved Duodenal Passage reconstruction

2.2.3. Oral Pouch with Preserved Duodenal Passage

After total gastrectomy and D2 lymphadenectomy a Roux limb is prepared from the first jejunal loop. Oral end of the loop is closed, pulled up to the oesophagus and fold over itself to create a J pouch, measuring 15 centimetres in length. A side to side manually sutured anastomosis is created to form the pouch. The apex of the J pouch is sutured to the oesophagus as an end to side oesophago-jejunostomy with one layer running suture. Approximately 50 cm far from the oesophago-jejunostomy the Roux limb is cut, but the mesentery is not touched. The oral end is sutured to the duodenum in an end to end manner, while the aboral end is sutured to the free end of Y limb, again end to end, to reconstruct the full passage (figure 5).

Figure 5: Oral Pouch with Preserved Duodenal Passage reconstruction

2.2.4. Roux-en-Y reconstruction

After performing the oesophagojejunostomy as in case of AP reconstruction, mentioned above, the Y anastomosis is created end to side manually with one layer running sutures, 50 cm distal to the oesophago-jejunal anastomosis (figure 6).

Figure 6: Roux-en-Y reconstruction

2.3. Methods of Assessment

2.3.1. Anthropometric Measures

The body weight and height were measured and the BMI (body mass index = weight (kg) / height (m²)) was calculated.

2.3.2. Laboratory Parameters

Blood samples were analysed for serum total protein (g/l), albumin (g/l), cholesterol (mmol/l) and triglyceride (mmol/l) levels, white blood count (G/l), absolute lymphocyte count (in one mm³), haemoglobin (g/l) and iron (µmol/l) levels, iron binding capacity was measured as transferrin saturation (%), immunoglobulin-A, immunoglobulin-G, immunoglobulin-M (g/l) and transferrin (g/l). Onodera's prognostic nutritional index (OPNI) was calculated as follows: serum albumin (g/l) x absolute lymphocyte count (/mm³) (71).

2.3.3. Motility Studies

Scintigraphic small bowel passage study (SSBP): Examinations were carried out with an MB 9101 gammacamera, in supine position

after ingestion of 5 ml semisolid test meal mixed with ^{99m}Tc labelled DTPA (diethylenetriamin-pentaacetate). During the one hour long examination images were obtained in every minutes. A standard region of interest (ROI) was placed to the upper left quadrant of the abdomen in every patient. A time activity curve was reproduced from the scintigraphic activity, detected above this ROI. The emptying rate was calculated from the curve and was expressed in %/minutes, which is a velocity dimension (72).

2.3.4. Absorption Studies

Lipid and carbohydrate absorption tests: Absorption of lipids was analysed by means of the Lipiodol test, while that of carbohydrates by the D-xylose absorption test. Each methods measure urinary excretion of non-metabolisable lipids or carbohydrates. Lipiodol test needs a 24 hour urine collection and the result is expressed in excreted milligrams of iodine (from Lipiodol, a lipid-soluble contrast material containing iodine) in the urine. During D-xylose test urine is collected for five hours in five samples and result is expressed as excreted milligrams of D-xylose (a non-metabolisable hexose).

2.3.5. Quality of Life Test

Gastrointestinal Quality of Life Index (GIQLI): The quality of life was determined by the GIQLI introduced by Eypasch (73) in 1994. This questionnaire consists of 36 questions concerning gastrointestinal complaints and physical and psychical well being during the last two weeks prior to the interview. Result of the test, the GIQL index describes quality of life as a value up to 144 points. Patients were requested to fill in the questionnaire by themselves, but a medical student was at hand in case patients had any problems with the test.

2.3.6. Additional Questionnaire

Attached to the quality of life test the questionnaire contained also an independent inquiry about the typical postgastrectomy complaints with the following questions:

1. Do you need to keep any dietary restrictions since surgery? If yes, what do you need to avoid?
2. Do you experience burning sensation in your chest or upper abdomen since surgery? If yes, what brings it about?
3. Do you experience any trouble with swallowing? If yes, for liquids or solids?
4. Which of the followings apply to your sense of hunger?
 - I am continuously hungry
 - I am hungry more often than before surgery
 - No change
 - I hardly ever feel hunger
 - I never feel hungry
5. Which of the followings apply to your appetite?
 - I enjoy eating
 - I eat only to stop feeling hungry
 - I eat only to avoid losing weight
6. How many times you eat in one day?
7. Can you take the same size of meal than before surgery or smaller?
8. Do you experience feeling sick or have you vomited since surgery?
9. How often you have loose stools since surgery?
10. Do you feel an uncomfortable feeling of fullness after a meal?
11. Do you feel light-headed or dizzy after a meal?
12. Do you feel an urge to lie down after a meal?

2.4. Clinical evaluation

2.4.1. Two weeks after surgery

Two weeks after total gastrectomy, before discharge from hospital, anthropometric, nutritional and immunologic laboratory measurements were carried out, as a basic data collection for later comparison.

2.4.2. 6, 12 and 24 months after surgery

Six, twelve and twenty-four months after surgery patients were admitted for a follow-up review. The anthropometric and laboratory measurements were repeated. Furthermore scintigraphic small bowel passage study, lipid and carbohydrate absorption tests were performed. The questionnaire with Eypash's gastrointestinal quality of life test and the additional questions about postgastrectomy symptoms were requested to be filled in at each follow-up.

2.4.3. Long term

After the 24 months follow-up patients were invited for a long term review every year until they turned up or proved to be drop outs.

During long term follow-up the same examinations were repeated, anthropometric and laboratory measurements, scintigraphic small bowel passage studies, lipid and carbohydrate absorption tests and quality of life interviews were performed.

2.5. Statistics and Ethics

Results are expressed as mean \pm SEM (standard error of mean) throughout the text, unless otherwise stated. Differences with a p value $<0,05$ were considered significant. Statistical analysis was performed with SPSS 11.5 software. Statistical significance for parametric variables were analysed by one way analysis of variance (One way ANOVA). Nonparametric variables were tested by Chi square test for comparison of two, Kruskal-Wallis test for comparison of more than two groups. When more than two (three) groups are compared, ANOVA or

Kruskal-Wallis test tell whether all groups can derive from the same population, or they are more likely belong to significantly different populations according to the tested parameter. If the latter applies, post hoc multiple comparison tests tell, which two groups were actually different from each other that much, that it reached statistical significance.

Study protocols were approved by the University of Pécs Ethics Committee. Informed consent was obtained from each patient.

3. Prospective, Randomised, Controlled Trial to compare Aboral Pouch to the standard Roux-en-Y Reconstruction (Trial-I)

3.1. Results

Anthropometric measurements: Results of the anthropometric measurements - body weight and body mass index (BMI) - postoperatively, 6 and 12 months after surgery are represented in table 8. There were no significant difference between the two groups according to the body weight and BMI.

Nutritional and immunologic laboratory measurements: Table 8 represents results of the laboratory measurements in the two groups. No significant difference has been found with serum total protein, albumin, triglyceride level, white blood count, haemoglobin, iron level, TIBC, immunoglobuline and transferrin measurements. Neither the OPNI calculated from the serum albumin and absolute lymphocyte count showed any difference. On the other hand the serum cholesterol level was significantly higher in the aboral pouch patients, than in the simple Roux-en-Y patients at the 12 month follow-up ($p < 0,01$).

Scintigraphic small bowel passage study (SSBP): The small bowel passage scintigraphy - determining the emptying rate of technecium-labelled test meal passing through the upper left quadrant of the abdomen, did not yield significantly different results comparing the two groups (table 9).

Lipid and carbohydrate absorption tests: The Lipiodol test proved significantly better lipid absorption in the aboral pouch group than in control Roux-en-Y group at the 6 months follow-up (table 9). Data at the 12 month follow-up showed also higher value at the pouch patients, but not significantly, likely because of the smaller patient number in the one year follow-up group. The carbohydrate absorption test did not yield significantly different results between the two groups.

Gastrointestinal Quality of Life Index (GIQLI): The quality of life, represented by the GIQLI according to Eypash yielded better results in the pouch group (table 9). Results of the questionnaire were 99,1 points at the 6 months and 103,6 points at the 12 months follow-up, while in

the control group 96,9 and 92,6 points respectively. The difference did not reach statistical significance though ($p = 0,061$ for 12 months results).

Postgastrectomy complaints: Approximately one third of the patients had to follow some dietary restrictions in both groups. In the pouch group intolerance to milk and dairy products - as a sign of lactose malabsorption - occurred in 14% of patients, while that in the control group more frequently, in 57% of the cases. Heartburn was observed in 25% in both groups, mild dysphagia at swallowing of liquid in around 50% without any difference between the two groups. Most patients felt constant or frequent hunger, which was realised sometimes more as a fatigue than normal hunger. This phenomenon was typical to all control patients, while 17% of the pouch patients reported no change in their sense of hunger. According to appetite, 50% of the control and 33% of the pouch patients observed lack of appetite. All patients in the control group and most of them in the pouch group said, that they can ingest a reduced amount of food per meals. Some pouch patients reported no change in the meal size. The number of meals taken per day was 4,25, significantly lower in the pouch group, than that in the control group (5,57) at the 6 months follow-up (table 9). Diarrhoea was complained 39% in the pouch group and 52% in the control group. Diarrhoea was more frequent as time went by in the control group, while its frequency did not change with time in the pouch group. Postprandial sickness was observed in 25-30% in both groups. Postprandial epigastric fullness and dumping was reported at least once in two weeks time in 70-70% of patients in both groups, and in both of them it became more frequent with time.

Table 8: Results of nutritional and laboratory measurements in Trial-I. Significant difference was found in serum cholesterol level at 12 months between AP and RY groups: * $p < 0,01$

Trial-I	Aboral pouch			Roux-en-Y		
	Follow-up:	Basic	6 months	12 months	Basic	6 months
n:	24	24	16	22	22	10
Body weight	65,02±3,9	63,28±4,2	62,91±4,3	60,00±2,0	60,53±2,6	57,16±3,1
BMI	22,94±1,2	22,01±1,1	22,43±1,2	21,66±0,8	21,88±0,7	21,71±0,8
Protein	60,15±1,5	70,75±2,1	71,48±1,2	64,91±1,8	69,58±2,1	69,66±2,6
Albumin	33,46±1,1	41,45±0,7	42,04±0,7	34,04±0,7	40,11±0,9	39,44±1,7
Triglyceride	1,71±0,1	1,35±0,1	1,33±0,2	1,73±0,1	1,38±0,1	1,2±0,1
Cholesterol	3,72±0,2	5,03±0,2	5,17±0,4*	4,29±0,2	4,97±0,3	3,84±0,1*
Haemoglobin	115,2±2,6	124,4±2,6	124,2±3,2	110,2±3,3	125,5±3,4	124,6±7,4
Iron	6,81±1,0	18,50±1,7	16,45±2,1	6,59±1,3	13,39±1,7	12,61±2,9
TIBC	46,19±3,8	53,82±3,1	55,15±3,5	46,94±1,5	51,25±4,4	43,20±2,3
Transferrine	1,96±0,1	2,91±0,1	2,88±0,2	1,93±0,1	2,68±0,1	2,61±0,2
Ig-A	2,26±0,3	2,16±0,2	2,28±0,2	2,88±0,3	2,24±0,4	2,42±0,7
Ig-G	8,88±0,7	10,70±0,6	10,90±0,7	9,70±0,7	11,55±0,7	12,32±1,0
Ig-M	1,68±0,3	1,83±0,3	1,13±0,2	1,16±0,4	0,82±0,3	1,14±0,4
OPNI	39,49±1,4	51,05±1,1	50,96±0,8	41,71±0,9	52,76±1,8	49,58±1,9

BMI: Body mass index, TIBC: Total iron binding capacity, OPNI: Onodera's prognostic nutritional index

Table 9: Results of motility, absorption and quality of life examinations in Trial-I. Significant differences were found in Lipiodol test results at 6 months between AP and RY groups: * $p < 0,05$, and in the number of meals taken per day at 6 months between AP and RY groups: ** $p < 0,01$.

Trial-I	Aboral pouch		Roux-en-Y	
	Follow-up:	6 months	12 months	6 months
n:	24	16	22	10
GIQLI	99,1±3,99	103,6±4,8	96,9±4,4	92,6±6,5
SSBP	0,95±0,25	0,64±0,14	0,50±0,14	0,99±0,39
Lipiodol test	2,46±0,3*	1,74±0,23	1,47±0,17*	1,52±0,18
Xylose test	malabsorption	malabsorption	malabsorption	malabsorption
No of meals / day	4,25±0,25**	4,58±0,31	5,57±0,29**	5,2±0,37

3.2. Discussion

A new type of gastric substitute - the Aboral Pouch - was introduced after total gastrectomy and compared to simple Roux-en-Y reconstruction in a prospective, randomised study.

Hypothetically the following advantages of aboral pouch construction over simple Roux-en-Y reconstruction were expected: 1) The passage slows down as a widened portion is formed in the small intestine with an antiperistaltic motility pattern. 2) The patients can eat larger meals, because of the enlarged reservoir capacity. 3) The absorption improves, since also the final 15 cm long portion of the Y limb takes part in the absorptive process.

Difficulties in maintaining body weight is well known in the literature of gastrectomy as a compulsory element of postgasterctomy syndrome. About 10-15% of the preoperative weight is usually lost (14,29). Pouch construction has been found to provide better weight recovery by Nakane (51) and Liedman (19), while others failed to prove any difference (49,53). In this study, patients in the pouch group lost 2,11 kg during the first postoperative year, while those in the control group 2,84 kg, which was 3,24 % weight loss in the pouch group and 4,73% in the control group, without any significant difference between the two groups. (In this study the body weight is compared not to the preoperative, but to the early postoperative body weight, which results in a lower percentage of loss!)

Nakane examined the serum nutritional parameters in simple Roux-en-Y, pouch plus Roux-en-Y and pouch plus interposition patients, and found the serum total protein and the Onodera's PNI significantly higher in the pouch plus Roux-en-Y group, while no difference in the serum albumin and cholesterol (51). Schwarz examined the haemoglobin and serum iron in postgastrectomy patients, and reported a considerable decrease in all but interposition patients, which has not been alleviated by pouch construction (53). In our study, in general, there was a significant increase in the measured nutritional and immunologic parameters – i.e. serum protein, albumin, hemoglobine, iron, immunoglobuline-G and OPNI - in all groups as time

passed by after surgery ($p < 0,005$), as it is well described in the literature (4,13).

Amongst the nutritional laboratory parameters measured in our patients in case of the serum cholesterol a significant difference could be demonstrated in favour of aboral pouch construction 12 months after surgery.

Most reports found a slower transit in patients undergone pouch construction, which is expected because of the reservoir construction itself (51,52). In our study small bowel passage scintigraphy according to Pellegrini's method failed to demonstrate any difference between pouch and non-pouch patients (72).

Lipid and carbohydrate absorption studies were carried out, which had not been performed earlier in a randomised trial after total gastrectomy. Significantly better lipid absorption has been found in favour of aboral pouch construction. The parallel occurrence of higher cholesterol level found in pouch group strengthens the hypothesis that the lipid absorption is improved by aboral pouch construction. The possible reason for this can be that the aborally positioned reservoir slows down the passage directly at that point where the bile and the pancreatic juice empty to the jejunum via the excluded Y limb, providing a better mix of food and digestive juices than in case of simple Roux-en-Y reconstruction.

The quality of life has not been found affected by pouch construction in some studies (50,53,65), while others found a positive impact (52,74). In Svedlund's reports the quality of life became improved as a long term consequence of pouch construction (74). He found that simple Roux-en-Y patients suffer from postalimentary symptoms throughout the follow-up period, gastric remnant after distal gastrectomy provides better adaptation to the end of the first year, but regarding the long term data patients with a pouch present with the highest quality of life. In our study differences in quality of life between patients with or without a pouch did not reach statistically significant levels. The significantly lower number of meals taken per day in patients

with Aboral Pouch, however seemed to reflect an advantage in reservoir capacity in favour of aboral pouch construction.

Among the advantages hypothetically expected from aboral pouch construction over simple Roux-en-Y reconstruction, the improved absorption seems to be proven in Trial-I. Additionally a tendency towards a better quality of life is suspected, for which beside the better absorption and lower number of meals taken per day, the fewer postgastrectomy symptoms, such as better tolerance to diary products, better appetite, fewer meals per day and less diarrhoea could be responsible.

4. Prospective, Randomised Trial to compare Aboral Pouch with Preserved Duodenal Passage, Aboral Pouch and Roux-en-Y Reconstructions after Total Gastrectomy (Trial-II)

4.1. Results

Basic parameters: There were no statistically significant differences showed in the early postoperative anthropometric and laboratory data, measured two weeks after surgery in the three groups (Table 10).

Table 10: Basic anthropometric and laboratory parameters in Trial-II. No significant difference was observed between the groups. P values for ANOVA are represented

Trial-II	AP	APwPDP	RY	p
n:	38	35	25	
Body weight (start)	63,56 ± 3,32	57,43 ± 1,49	64,92 ± 2,13	0,19
BMI (start)	22,79 ± 1,06	20,99 ± 0,79	22,76 ± 0,74	0,41
Protein (start)	61,76 ± 1,83	66,15 ± 2,89	64,99 ± 1,79	0,29
Albumin (start)	33,39 ± 1,15	34,85 ± 2,09	34,24 ± 0,80	0,73
Triglicerid (start)	1,74 ± 0,14	1,58 ± 0,17	1,71 ± 0,14	0,78
Cholesterol (start)	3,82 ± 0,21	4,68 ± 0,33	4,17 ± 0,29	0,13
Hemoglobin (start)	112,35 ± 2,51	120,53 ± 5,23	119,08 ± 2,78	0,14
Iron (start)	6,61 ± 0,92	9,96 ± 2,12	6,58 ± 1,18	0,17
Transferrine sat % (start)	7,60 ± 1,42	13,40 ± 7,90	15,20 ± 5,50	0,50
Transferrine (start)	1,98 ± 0,13	2,16 ± 0,17	1,94 ± 0,09	0,52
IgA (start)	2,39 ± 0,28	2,44 ± 0,39	2,82 ± 0,31	0,59
IgG (start)	9,31 ± 0,62	8,69 ± 0,96	9,28 ± 0,71	0,82
IgM (start)	1,66 ± 0,31	1,43 ± 0,3	1,15 ± 0,34	0,51
OPNI (start)	39,57 ± 1,54	44,03 ± 2,55	41,95 ± 0,99	0,18

Anthropometric measurements: Results of the anthropometric measurements - body weight, body mass index (BMI) and change in BMI in percentage of the postoperative BMI – 6, 12 and 24 months after surgery are represented in table 11. No significant difference has been found in anthropometric parameters comparing the three groups. Body weight was fairly stable in all three groups during follow-up (Figure 7), remarkably though the change in BMI was the most consequent in APwPDP group, data raised and remained above 100% throughout the

observation period, with the highest, but still not significant difference in favour of APwPDP 12 months after surgery (Figure 8).

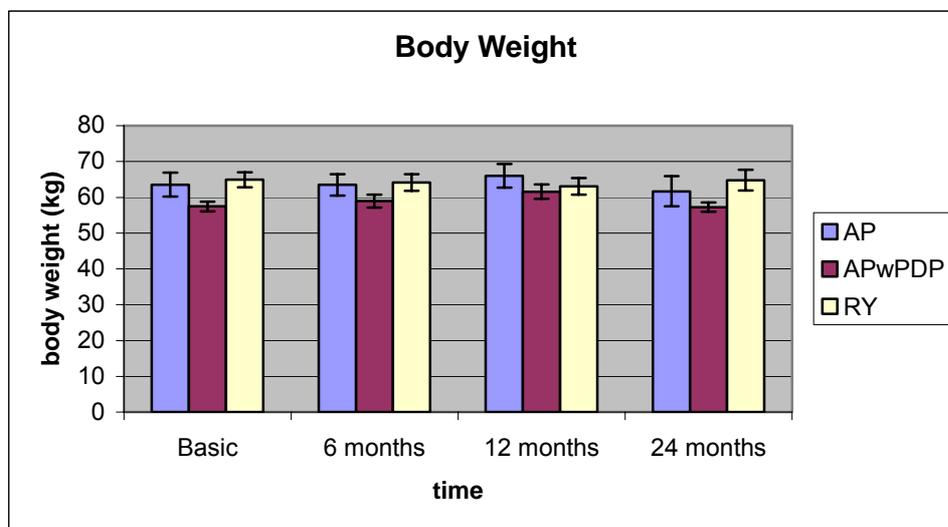


Figure 7: Results of body weight measurements

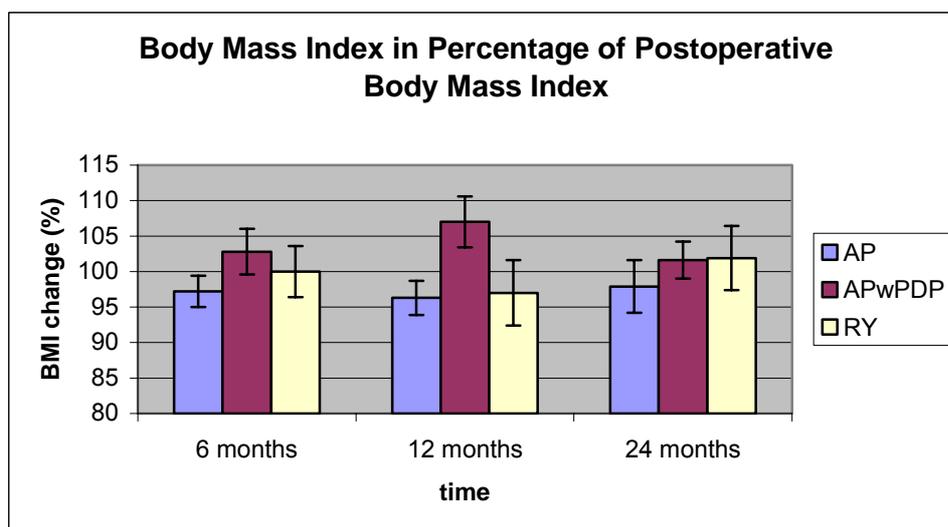


Figure 8: Change in body mass index results

Table 11: Results of measurements in Trial-II. Significant differences were found in serum cholesterol at 12 months between, in serum iron at 6 and 12 months, in transferrine saturation at 12 months, in GIQL index at 12 months, in small bowel passage at 6 and 24 months, in results of the Lipiodol test at 12 months and in the number of meals taken per day at 6 and 12 months between the groups. P values for ANOVA are represented. Post hoc test results revealing the source of difference are detailed in the text

Trial-II	AP	APwPDP	RY	p
n:	38	35	25	
Body weight – 6 months	63,50 ± 3,06	58,94 ± 1,88	64,13 ± 2,39	0,40
Body weight – 12 months	66,00 ± 3,33	61,60 ± 2,00	63,08 ± 2,38	0,54
Body weight – 24 months	61,68 ± 4,23	57,22 ± 1,32	64,80 ± 2,98	0,29
BMI – 6 months	22,30 ± 0,98	21,04 ± 0,55	22,18 ± 0,68	0,53
BMI – 12 months	23,06 ± 0,92	21,87 ± 0,57	22,27 ± 0,61	0,54
BMI – 24 months	21,92 ± 1,28	21,65 ± 0,64	23,59 ± 0,69	0,34
BMI % – 6 months	97,23 ± 2,22	102,82 ± 3,27	100,00 ± 3,64	0,23
BMI % – 12 months	96,73 ± 2,46	107,01 ± 3,61	97,07 ± 4,67	0,16
BMI % – 24 months	97,96 ± 3,78	101,64 ± 2,62	101,91 ± 4,57	0,24
Protein – 6 months	70,94 ± 1,54	73,28 ± 1,30	70,50 ± 1,55	0,47
Protein – 12 months	73,03 ± 1,12	72,74 ± 1,38	70,03 ± 1,43	0,84
Protein – 24 months	76,04 ± 1,87	74,63 ± 0,75	74,70 ± 1,73	0,75
Albumin – 6 months	40,97 ± 0,60	40,90 ± 0,49	40,50 ± 0,65	0,84
Albumin – 12 months	41,99 ± 0,65	41,89 ± 0,60	40,79 ± 0,98	0,48
Albumin – 24 months	43,7 ± 0,86	42,46 ± 0,70	44,15 ± 0,80	0,31
Triglicerid – 6 months	1,34 ± 0,14	1,33 ± 0,14	1,40 ± 0,10	0,93
Triglicerid – 12 months	1,52 ± 0,24	1,27 ± 0,12	1,37 ± 0,12	0,64
Triglicerid – 24 months	1,45 ± 0,26	1,38 ± 0,23	1,46 ± 0,15	0,97
Cholesterol – 6 months	4,90 ± 0,17	4,97 ± 0,23	4,75 ± 0,25	0,78
Cholesterol – 12 months	5,00 ± 0,29	5,42 ± 0,28	4,53 ± 0,11	0,05
Cholesterol – 24 months	5,49 ± 0,39	5,65 ± 0,28	5,12 ± 0,24	0,53
Hemoglobin – 6 months	124,18 ± 2,31	128,35 ± 3,65	125,25 ± 2,78	0,62
Hemoglobin – 12 months	122,55 ± 2,85	130,69 ± 2,97	126,47 ± 3,30	0,21
Hemoglobin – 24 months	121,81 ± 5,31	133,23 ± 3,27	132,40 ± 3,80	0,08
Iron – 6 months	17,75 ± 1,80	17,97 ± 1,22	13,26 ± 1,37	0,03
Iron – 12 months	18,57 ± 2,08	22,54 ± 2,07	13,84 ± 1,53	0,01
Iron – 24 months	17,30 ± 3,15	22,49 ± 1,29	18,60 ± 2,76	0,29
Transferrine % – 6 mo.	29,32 ± 4,51	21,41 ± 4,83	19,52 ± 3,01	0,20
Transferrine % – 12 mo.	38,05 ± 10,30	32,45 ± 4,51	20,30 ± 2,29	0,05
Transferrine % – 24 mo.	37,10 ± 11,05	30,03 ± 2,34	35,40 ± 10,01	0,66
Transferrine – 6 months	2,76 ± 0,12	2,82 ± 0,17	2,68 ± 0,13	0,80
Transferrine – 12 months	2,84 ± 0,16	2,89 ± 0,20	2,77 ± 0,15	0,90
Transferrine – 24 months	2,80 ± 0,22	3,17 ± 0,16	3,08 ± 0,22	0,38
IgA – 6 months	2,53 ± 0,24	3,09 ± 0,47	2,49 ± 0,30	0,42
IgA – 12 months	2,88 ± 0,32	2,58 ± 0,62	2,91 ± 0,42	0,89
IgA – 24 months	3,21 ± 0,66	3,53 ± 0,49	2,12 ± 0,43	0,21
IgG – 6 months	10,71 ± 0,45	12,07 ± 0,94	11,51 ± 0,56	0,29
IgG – 12 months	11,81 ± 0,63	9,82 ± 1,09	11,82 ± 0,52	0,17
IgG – 24 months	11,82 ± 1,06	12,10 ± 0,89	11,87 ± 1,08	0,97
IgM – 6 months	1,09 ± 0,67	0,98 ± 0,12	0,92 ± 0,09	0,35
IgM – 12 months	1,14 ± 0,15	1,31 ± 0,35	1,32 ± 0,23	0,78
IgM – 24 months	1,69 ± 0,29	1,63 ± 0,27	1,80 ± 0,51	0,94
OPNI – 6 months	53,48 ± 1,46	51,94 ± 1,36	52,15 ± 1,34	0,70
OPNI – 12 months	53,89 ± 1,65	53,95 ± 1,68	51,74 ± 1,16	0,50
OPNI – 24 months	54,03 ± 1,64	54,61 ± 1,52	54,59 ± 1,68	0,95
GIQLI – 6 months	102,38 ± 3,31	103,25 ± 3,85	93,90 ± 4,15	0,16
GIQLI – 12 months	97,83 ± 4,62	108,93 ± 3,43	93,59 ± 5,10	0,05

GIQLI – 24 months	101,36 ± 4,74	106,22 ± 6,13	99,30 ± 5,09	0,65
SSBP – 6 months	0,82 ± 0,17	0,29 ± 0,07	0,50 ± 0,09	0,03
SSBP – 12 months	0,58 ± 0,10	0,57 ± 0,13	0,79 ± 0,16	0,43
SSBP – 24 months	0,62 ± 0,10	0,41 ± 0,11	0,81 ± 0,12	0,05
Lipiodol – 6 months	2,45 ± 0,23	2,01 ± 0,67	1,85 ± 0,29	0,30
Lipiodol – 12 months	2,52 ± 0,28	2,94 ± 0,20	2,15 ± 0,11	0,02
Lipiodol – 24 months	2,31 ± 0,34	2,91 ± 0,39	2,41 ± 0,31	0,37
Xylose – 6 months	1351,5 ± 205	1431,5 ± 340	993,3 ± 139	0,38
Xylose – 12 months	1226,5 ± 207	1408,7 ± 373	1080,7 ± 161	0,65
Xylose – 24 months	1162,2 ± 261	1308,8 ± 171	1524,1 ± 303	0,60
No of meals – 6 months	5,12 ± 0,36	4,79 ± 0,21	5,92 ± 0,30	0,05
No of meals–12 months	4,75 ± 0,26	4,85 ± 0,29	6,19 ± 0,37	0,004
No of meals – 24 months	4,89 ± 0,26	5,13 ± 0,35	6,56 ± 0,81	0,08

Transferrin %: transferrin saturation in percentage, No of meals: number of meals taken per day

Nutritional and immunologic laboratory measurements: Amongst the measured nutritional parameters no significant difference were found regarding serum total protein, albumin, triglyceride, haemoglobin, transferrine, immunoglobulines and OPNI among the groups (table 11). Regarding serum cholesterol a significant difference was detected (ANOVA $p = 0,05$), it was significantly higher in APwPDP group compared to control Roux-en-Y (post hoc test $p = 0,029$) as well as in AP group compared to control Roux-en-Y (post hoc test $p = 0,049$) at the 12 months follow-up (Figure 9).

Serum iron showed differences among the groups at 6 months (ANOVA $p = 0,03$) as well as at 12 months (ANOVA $p = 0,01$). Post hoc test showed that serum iron at 6 months in AP group was higher than in RY ($p = 0,015$) as well as in APwPDP higher than in RY ($p = 0,045$). At the 12 months follow-up APwPDP results were significantly higher than RY results ($p = 0,04$) (Figure 10). Very well in concordance with it, serum transferrine saturation – a parameter reflecting iron metabolism – was also significantly different among the groups at the 12 months follow-up (ANOVA $p = 0,05$): AP was significantly higher than RY ($p = 0,02$) and APwPDP was significantly higher than RY ($p = 0,04$).

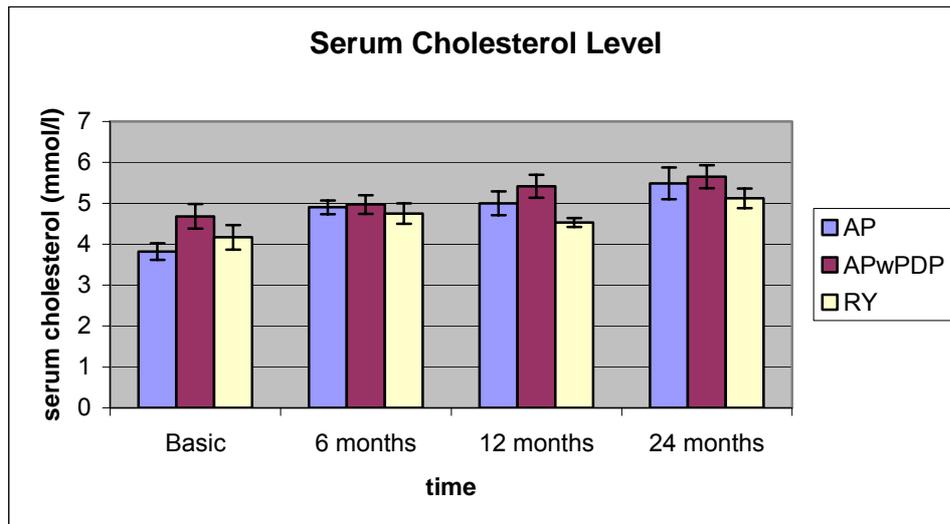


Figure 9: Results of serum cholesterol measurements

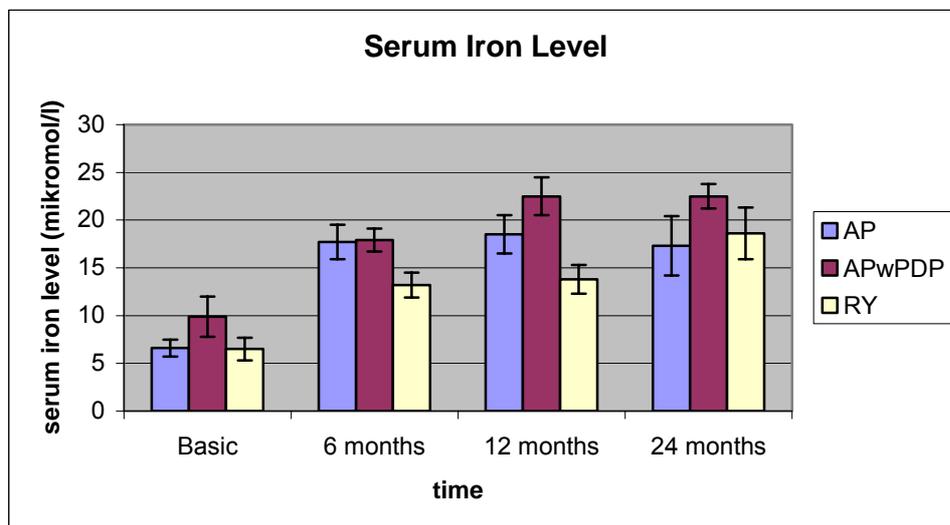


Figure 10: Results of serum iron measurements

Scintigraphic small bowel passage study (SSBP): Small bowel passage scintigraphy by determining the emptying rate of technecium-labelled test meal passing through the upper left quadrant of the abdomen, found the slowest emptying rate in APwPDP patients, the fastest in AP patients at 6 months and in RY patients at 12 and 24 months (Figure 11). The differences reached statistical significance at 6 months (ANOVA $p = 0,03$) and at 24 months (ANOVA $p = 0,05$). Post hoc test showed the origin of difference being between AP and

APwPDP groups at 6 months ($p = 0,017$) and between RY and APwPDP group at 24 months ($p = 0,047$) (Figure 11).

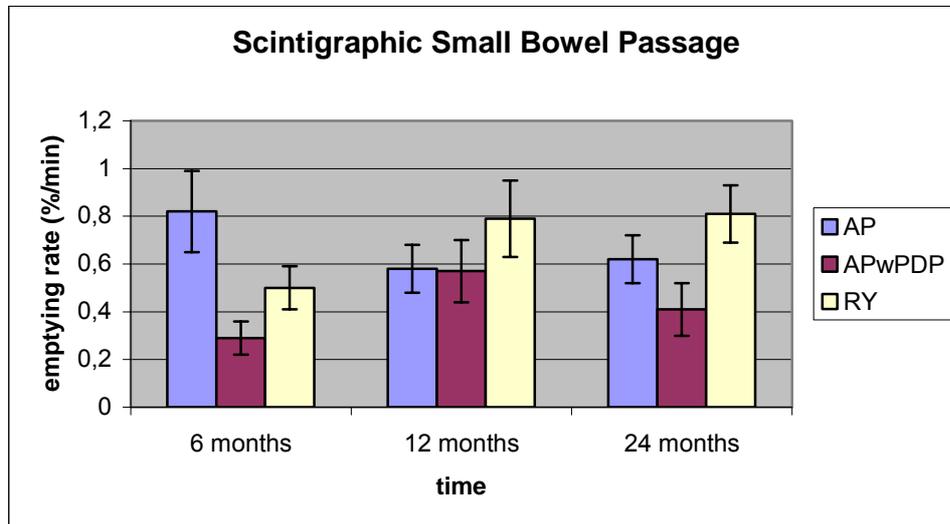


Figure 11: Results of scintigraphic small bowel passage studies

Lipid and carbohydrate absorption tests: The Lipiodol test proved significantly better lipid absorption in APwPDP group than in control RY group as well as in AP group compared to RY group at the 12 months follow-up (ANOVA $p = 0,02$, post hoc APwPDP vs RY $p = 0,012$, post hoc AP vs RY $p = 0,032$) (figure 12, table 11). Data at 6 month showed best absorption for AP, but high standard deviation in all groups precluded showing any real difference (Figure 12). Carbohydrate absorption test did not reveal any significant difference among the groups.

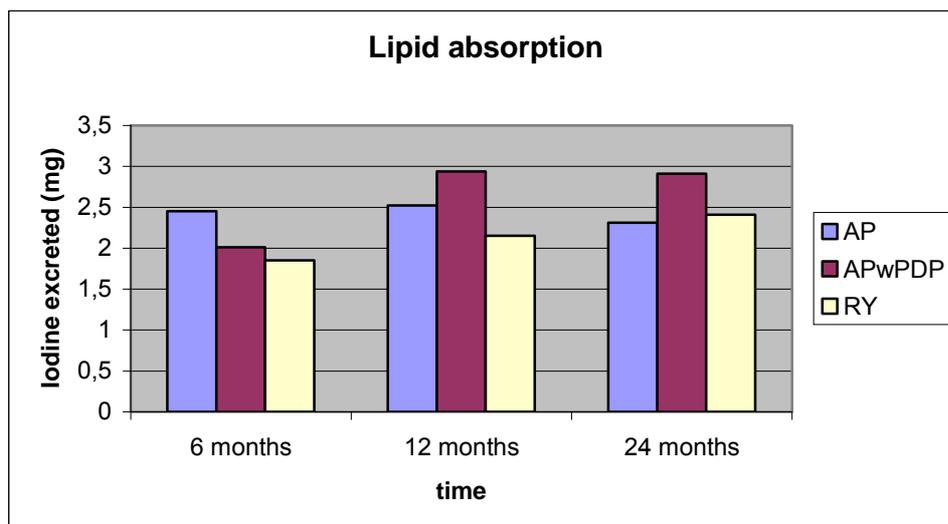


Figure 12: Results of lipid absorption tests

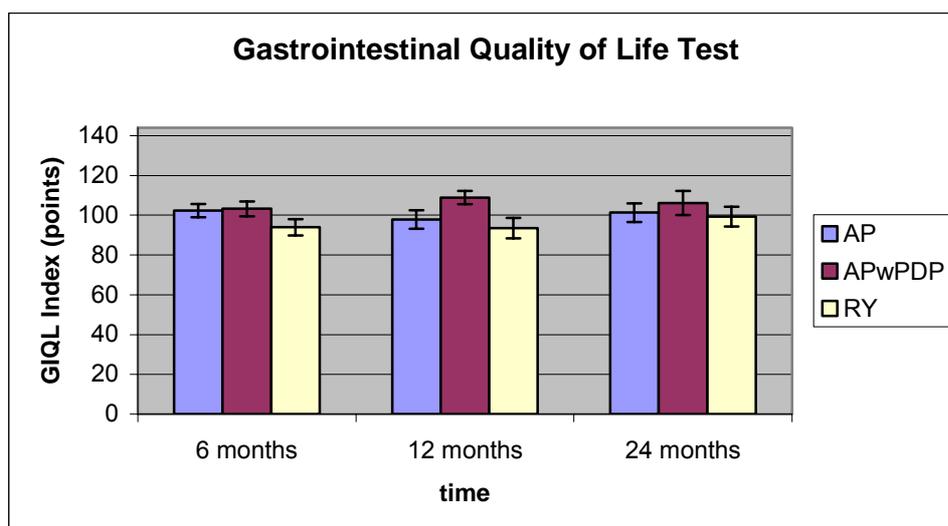


Figure 13: Results of quality of life measurements

Quality of Life: The quality of life -represented by the GIQLI – was the highest in APwPDP group throughout the examination period, lowest in RY and somewhere in between in AP (Figure 13). The differences reached statistical significance though only at 12 months follow-up (ANOVA $p = 0,05$). Post hoc multiple comparisons showed, that APwPDP results differed the most from RY ($p = 0,024$). The number of meals taken per day – as a representative of reservoir capacity, thus quality of life and somewhat of motility too – differed

significantly among the groups at 6 as well as at 24 months (ANOVA $p = 0,05$ and $p = 0,008$). It was high, around 6/day in RY patients and almost equally low, between 4-5, in patients with aboral pouch (AP as well as APwPDP), independent of preservation of duodenal passage. Post hoc comparisons showed significant difference between RY and APwPDP at 6 months ($p = 0,018$), RY and AP ($p = 0,002$) and RY and APwPDP ($p = 0,006$) at 12 months (Figure 14).



Figure 14: The number of meals taken per day

4.2. Discussion

Regarding the primary endpoints, Trial-II has revealed a little difference in favour of duodenal passage preservation. Body weight – as in the present trial - was not found positively influenced by a more complicated reconstruction, especially in the short term (53, 65). Nakane found better weight-gain in pouch patients at 24 months and Liedmann at 96 months after surgery (19, 51).

Though no significant difference has been demonstrated in body weight and other anthropometric measures, the quality of life, measured by Eypash's GIQLI (gastrointestinal quality of life index) was significantly higher in APwPDP group at 12 months – but not at 6 and 24 months - after surgery compared to controls.

Quality of life was found to be unaffected by pouch construction in some trials (53, 65), this was the case also in Trial-II. Interposition on the other hand influenced quality of life positively in Trial-II and in some other studies (53). In Fuchs' study comparing Roux-en-Y plus pouch to interposition plus pouch no significant difference was revealed using Visick score and Spitzer index, which both are not specific to gastrointestinal, especially to postgastrectomy symptoms (65). In general in those studies where a quality of life advantage was demonstrated, the measuring tool was more specific for gastrointestinal symptoms.

The number of meals taken per day is a limited measure of well being or quality of life. Patients with a pouch, regardless of preservation of the duodenal passage, did better throughout the observation period in this sense. The average number of meals taken was below five in AP and APwPDP patients while above six in RY.

Regarding secondary endpoints most nutritional and immunologic laboratory parameters were independent of the reconstruction method chosen. Cholesterol though - as in Trial-I - was an exception. A higher cholesterol level was demonstrated in patients with APwPDP as well as in AP reconstruction when compared to RY, 12 months after surgery. Other important significant difference in favour of duodenal passage preservation was the higher serum iron level compared to controls at 6 as well as 12 months after surgery. Regarding iron level a significant difference was demonstrated in favour of pouch construction also, but only at 6 months and less than with duodenal passage preservation. Well in concordance with iron level changes, serum transferrine saturation was also significantly higher in APwPDP compared to control as well as in AP compared to control.

Cholesterol was rarely measured in randomised studies comparing different reconstruction types. Nakane found no difference in serum cholesterol level between Roux-en-Y, Roux-en-Y plus pouch and interposition plus pouch patients 12 to 64 months postoperatively (51).

Iron getting absorbed in the duodenum is not surprisingly higher in patients with preserved duodenal passage. This was found also by

Schwarz et al comparing five reconstruction types, i.e. the standard Roux-en-Y and two different sizes of pouches with or without duodenal passage preservation (53). The better absorption of iron in case of duodenal passage preservation must help to alleviate the anaemic tendency after gastrectomy. Blood haemoglobin concentration results support this idea, showing higher levels at APwPDP reconstruction throughout, compared to the other two groups, although not significantly (table 11).

Motility of the gastric substitute was measured by different means in different studies. Most investigators, as ourselves, used scintigraphic imaging of a Technecium labelled test meals and expressed results as emptying time (51, 59) or in %/minute giving the speed of passage (60, 72). In a most recently published randomised study a more elaborated technique, intestinal manometry was used (62). In our results APwPDP reconstruction showed the slowest emptying at 6 and 12 months compared to RY and AP reconstruction. As the ROI (Region of Interest) is placed above the left upper quadrant of the abdomen, scintigraphy measures the jejunum interposition part in APwPDP patients. Dumping type of emptying was often seen in RY and AP patients. Others using scintigraphy showed no difference in emptying time between RY, RY plus pouch and interposition plus pouch (51), neither between two double tract methods (59). With manometry a healthier passage pattern was demonstrated with propagating peristaltic waves (phase III motor activity) in case of Longmire type jejunum interposition when compared to the interposition of a jejunal pouch (62). This latter supports the hypothesis that the pouch having been cut alongside the jejunal wall cannot propel food correctly.

Absorption studies have not been performed in randomised trials. Trial-II failed to demonstrate any advantage of a more complicated reconstruction in carbohydrate absorption but lipid absorption – measured by the Lipiodol test - proved significantly better at 12 months in case of duodenal passage preservation, as well as with pouch construction at a lesser magnitude (table).

Altogether the superiority of duodenal passage preservation has been proven over simple Roux-en-Y or AP reconstruction in serum iron level and transferrine saturation, serum cholesterol level, lipid absorption, motility and quality of life 12 months after surgery. Most differences disappeared by 24 months postoperatively. Superiority of aboral pouch construction itself over Roux-en-Y was also proven in lipid absorption, serum cholesterol, serum iron level and the number of meals taken per day, however results of AP reconstruction always remained below that of APwPDP reconstruction.

5. Long Term Results in comparing Aboral Pouch with Preserved Duodenal Passage, Aboral Pouch and Roux-en-Y Reconstructions after Total Gastrectomy

5.1. Long Term Results

Thirty-five patients were available at least 3 years – twenty-three 3 years, eight 4 years, three 5 years and one 6 years - after surgery. The average follow-up was 3,48 years after total gastrectomy. Thirteen patients from AP, twelve from APwPDP and ten from RY groups attended for long term examinations.

Anthropometric measurements: The body weight, BMI as well as change in BMI in percentage of the postoperative BMI did not differ among the groups at the long term check-up (table 12, figure 15). Patients in APwPDP group gained the most weight, their BMI was 7% higher than postoperatively, but the difference between the groups was not significant.

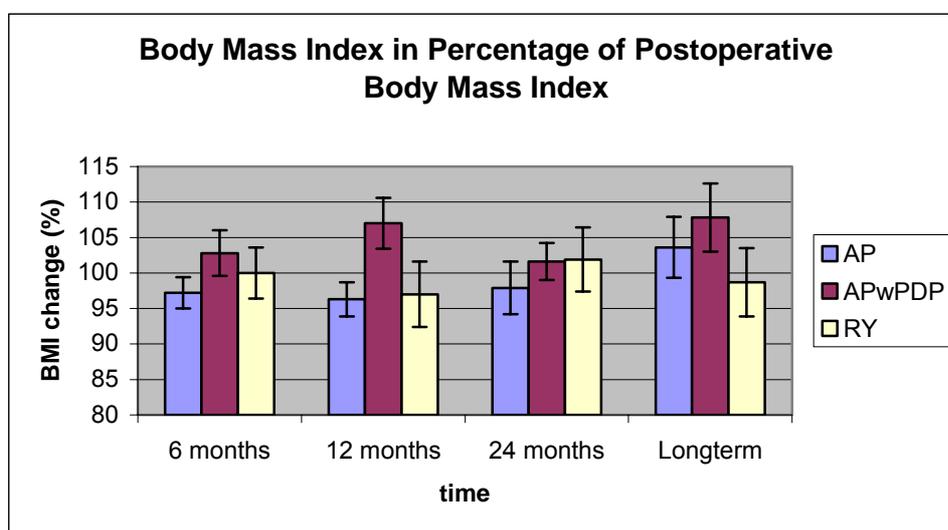


Figure 15: Body mass index change results

Table 12: Long term results: In the long run significant differences were found between the groups in small bowel passage and the number of meals taken per day. P values for ANOVA are represented. Post hoc test results revealing the source of difference are detailed in the text

Long Term	AP	APwPDP	RY	p
n:	13	12	10	
Body weight	73,10 ± 7,92	61,70 ± 2,21	66,80 ± 5,41	0,24
BMI	24,91 ± 2,30	22,36 ± 0,75	24,74 ± 1,21	0,32
BMI %	103,69 ± 4,32	107,88 ± 4,87	98,75 ± 4,82	0,43
Protein	77,00 ± 1,75	73,72 ± 1,27	73,34 ± 2,10	0,23
Albumin	44,86 ± 0,77	43,97 ± 0,64	43,54 ± 1,01	0,51
Triglycerid	1,69 ± 0,38	1,51 ± 0,25	1,22 ± 0,16	0,62
Cholesterol	5,57 ± 0,37	5,00 ± 0,18	4,96 ± 0,29	0,25
Hemoglobin	135,77 ± 2,57	134,64 ± 2,56	131,71 ± 6,66	0,75
Iron	20,14 ± 2,53	24,15 ± 2,54	19,9 ± 2,90	0,43
Transferrine saturation %	27,86 ± 7,62	33,13 ± 18,15	23,48 ± 5,82	0,79
Transferrine	2,68 ± 0,12	2,98 ± 0,09	2,24 ± 0,22	0,36
IgA	3,88 ± 0,69	3,07 ± 0,46	2,43 ± 0,52	0,27
IgG	12,83 ± 1,11	11,40 ± 0,97	10,91 ± 1,06	0,45
IgM	2,15 ± 0,40	1,37 ± 0,19	1,36 ± 0,57	0,22
OPNI	55,13 ± 1,56	55,38 ± 1,17	51,38 ± 1,69	0,21
GIQLI	94,38 ± 6,86	96,20 ± 6,53	94,6 ± 9,64	0,98
SSBP	0,92 ± 0,14	0,54 ± 0,08	0,76 ± 0,13	0,04
Lipiodol	4,06 ± 0,83	4,49 ± 0,41	4,42 ± 0,58	0,78
Xylose	843,5 ± 186	1036,2 ± 157	1133,8 ± 306	0,61
Number of meals / day	4,25 ± 0,41	4,30 ± 0,26	6,80 ± 0,49	0,0001

Nutritional and immunologic laboratory measurements: In the long term no difference could be detected in the examined laboratory parameters - i.e. serum total protein, albumin, triglycerid, cholesterol, haemoglobin, iron, transferrine saturation, transferrine, immunoglobulins and OPNI – among the three groups (table 12).

Scintigraphic small bowel passage study (SSBP): Small bowel passage scintigraphy showed the slowest emptying rate in patients with APwPDP reconstruction in the long term too. The difference for the three groups was significant (ANOVA $p = 0,04$), post hoc comparison revealed significant difference between AP and APwPDP being responsible for it ($p = 0,029$) (Figure 16).

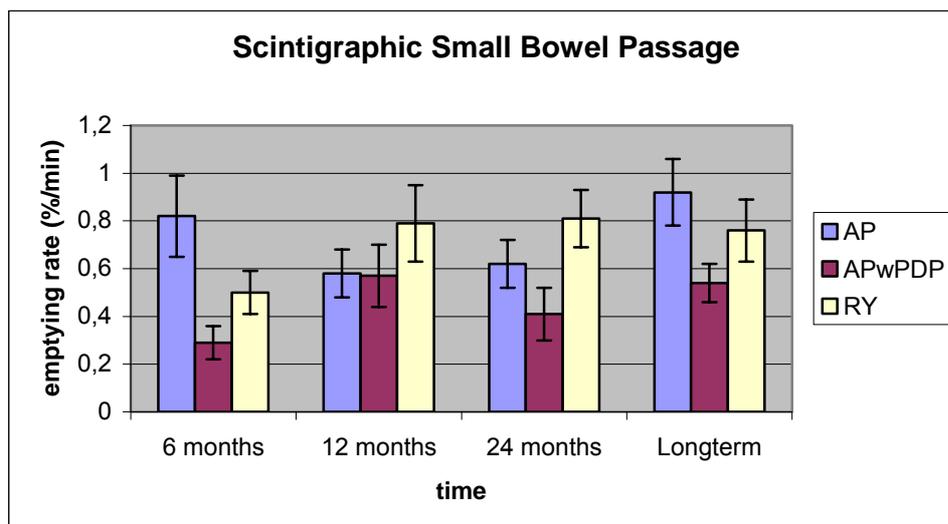


Figure 16: Results of small bowel passage studies

Lipid and carbohydrate absorption tests: No reconstruction dependent difference has been detected regarding lipid and carbohydrate absorption in the long term (table 12).

Quality of Life: Result of the gastrointestinal quality of life test did not reveal any significant difference among the three groups. The number of meals taken per day however still differed in favour of reconstructions with a pouch (ANOVA $p = 0,0001$, post hoc comparisons: RY versus AP $p = 0,0001$, RY versus APwPDP $p = 0,0001$) (Figure 17).

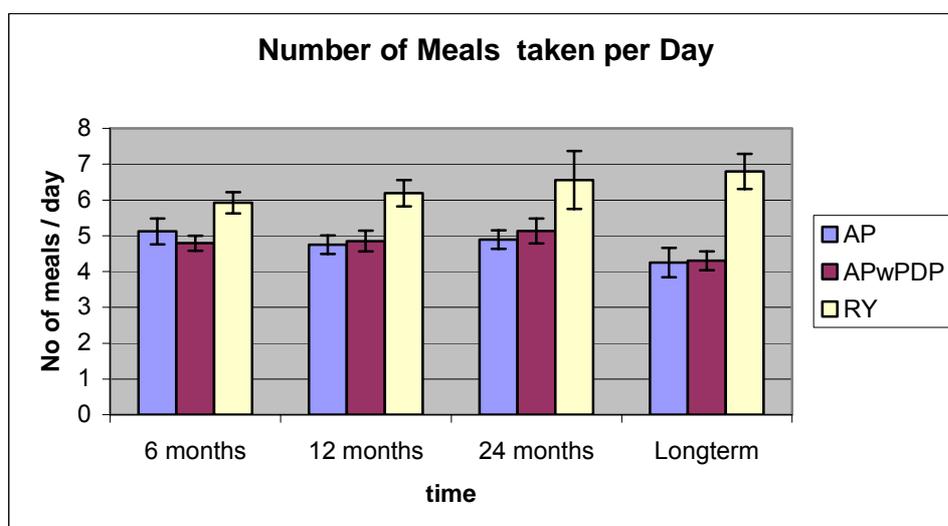


Figure 17: Number of meals taken per day

5.2. Discussion

Most of the differences seen in Trial-II disappeared in the long term, as it could have been judged already from the 24 months data. No advantage was gained from aboral pouch construction in the long term, apart from the lower number of meals taken per day, but it did not translate into a gain in the quality of life. Duodenal passage preservation did not yield an advantage in nutritional or quality of life parameters, neither in the long term, nor in absorption of lipids, however a favourable rate of emptying – i.e. a slower emptying rate – remained as an advantage even after 3 years postoperatively.

Long term follow-up of randomised population of different reconstructions after total gastrectomy are rare. Iivonen et al reported better quality of life in pouch patients compared to Roux-en-Y 5 years after surgery (55). Kono et al found better quality of life and less bile reflux in cases of pouch construction compared to simple Roux-en-Y reconstruction 4 years after surgery (61). Mochiki et al described a favourable motility pattern and a better food intake (volume per meal) for Longmire interposition, compared to oral pouch interposition 44 months after total gastrectomy (62).

In Trial-II long term follow-up showed, that - apart from a favourably slower transit with preserved duodenal passage and lower number of meals with pouch construction - no long lasting advantage can patients expect from a more complicated reconstruction. The important advantages in lipid and iron metabolism and quality of life however, seen in the first years after gastrectomy may give a very important nutritional support to these patients in the fight of cancer in the most sensitive years, when recurrence is most frequent. Although no data of ours or else supports this oncological advantage of duodenal passage preservation or pouch construction yet.

6. Randomised Comparison of Aboral Pouch with Preserved Duodenal Passage to Oral Pouch with Preserved Duodenal Passage (Trial-III)

6.1. Results

Regarding the postoperative, basic anthropometric and laboratory parameters no significant difference has been demonstrated between Aboral Pouch with Preserved Duodenal Passage (APwPDP) and Oral Pouch with Preserved Duodenal Passage (OPwPDP) patients (table 13).

Table 13: Basic anthropometric and laboratory parameters in Trial-III

Trial-III	APwPDP	OPwPDP	p
N:	14	13	
Body weight (start)	61,33 ± 1,72	66,10 ± 1,97	0,08
BMI (start)	22,57 ± 0,57	24,19 ± 0,62	0,07
Protein (start)	65,09 ± 2,85	64,97 ± 2,53	0,97
Albumin (start)	33,05 ± 1,58	35,41 ± 1,76	0,32
Triglycerid (start)	1,75 ± 0,18	1,99 ± 0,22	0,40
Cholesterol (start)	4,93 ± 0,35	4,78 ± 0,25	0,74
Hemoglobin (start)	113,24 ± 5,57	114,39 ± 3,76	0,87
Iron (start)	8,35 ± 2,05	7,77 ± 1,36	0,82
Transferrine sat % (start)	9,70 ± 3,33	14,57 ± 2,27	0,25
Transferrine (start)	2,30 ± 0,19	2,03 ± 0,20	0,35
IgA (start)	2,61 ± 0,46	3,00 ± 0,38	0,54
IgG (start)	8,37 ± 0,97	9,02 ± 0,78	0,62
IgM (start)	1,18 ± 0,24	1,55 ± 0,19	0,26
OPNI (start)	43,84 ± 1,78	45,83 ± 3,69	0,62

Anthropometric measurements: As represented in table 13 and figure 18, 19, no significant difference has been found in body weight, body mass index (BMI) and change in BMI in percentage of the postoperative BMI 6, 12 and 24 months after surgery between groups APwPDP and OPwPDP.

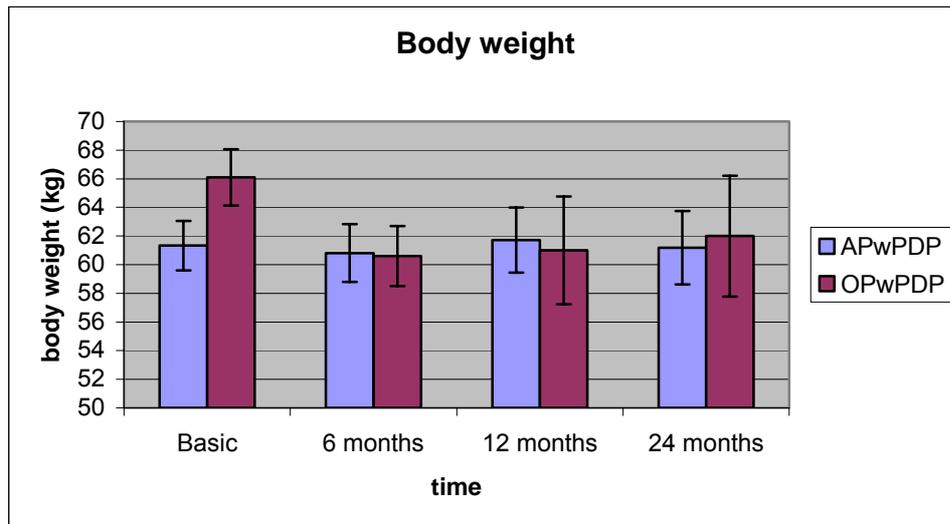


Figure 18: Results of body weight measurements

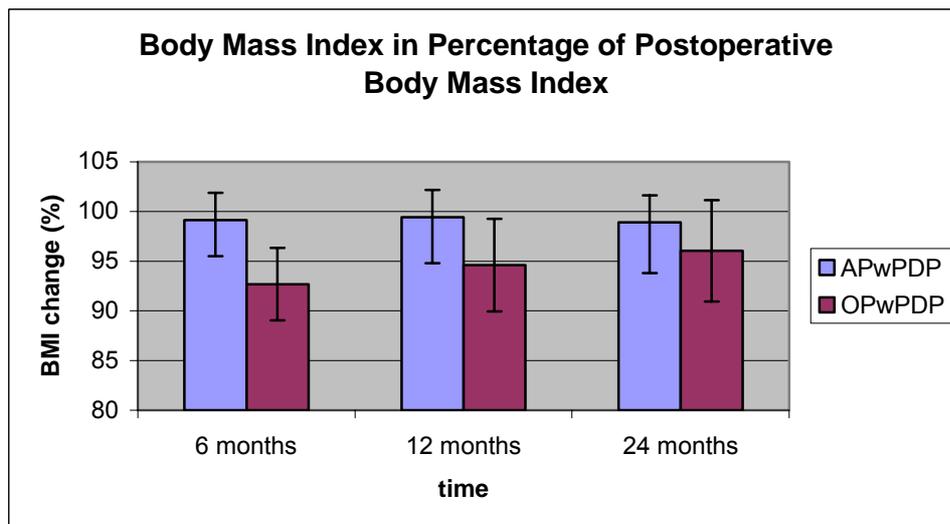


Figure 19: Body mass index change results

Table 14: Results of nutritional, laboratory, motility, absorption and quality of life measurements in Trial-III. Significant differences were found in serum protein level at 6 months, serum albumin at 6, 12 and 24 months, immunoglobuline-A level at 24 months and in the number of meals taken per day at 6 months. P values for ANOVA are represented. Post hoc test results revealing the source of difference are detailed in the text

Trial-III	APwPDP	OPwPDP	p
N:	14	13	
Body weight – 6 months	60,81 ± 2,02	60,60 ± 2,09	0,95
Body weight – 12 months	61,71 ± 2,27	61,00 ± 3,76	0,86
Body weight – 24 months	61,18 ± 2,57	62,00 ± 4,22	0,86
BMI – 6 months	22,31 ± 0,55	22,22 ± 0,73	0,92
BMI – 12 months	22,68 ± 0,71	22,68 ± 0,97	0,99
BMI – 24 months	23,13 ± 0,97	22,66 ± 1,17	0,76
BMI % – 6 months	99,14 ± 2,76	92,69 ± 3,63	0,16
BMI % – 12 months	99,43 ± 2,74	94,61 ± 4,65	0,38
BMI % – 24 months	98,91 ± 2,72	96,05 ± 5,11	0,64
Protein – 6 months	73,22 ± 1,34	69,81 ± 0,74	0,05
Protein – 12 months	72,92 ± 1,29	72,18 ± 1,66	0,72
Protein – 24 months	74,63 ± 0,75	74,70 ± 1,73	0,61
Albumin – 6 months	41,50 ± 0,71	43,89 ± 1,01	0,05
Albumin – 12 months	42,10 ± 0,71	45,04 ± 1,26	0,04
Albumin – 24 months	42,76 ± 0,72	47,37 ± 1,55	0,007
Triglicerid – 6 months	1,32 ± 0,15	1,43 ± 0,16	0,61
Triglicerid – 12 months	1,32 ± 0,12	2,00 ± 0,65	0,23
Triglicerid – 24 months	1,38 ± 0,22	1,30 ± 0,16	0,79
Cholesterol – 6 months	5,14 ± 0,24	5,09 ± 0,22	0,89
Cholesterol – 12 months	5,46 ± 0,28	4,71 ± 0,36	0,11
Cholesterol – 24 months	5,69 ± 0,26	5,19 ± 0,30	0,24
Hemoglobin – 6 months	126,57 ± 4,02	125,18 ± 3,81	0,80
Hemoglobin – 12 months	128,00 ± 4,11	130,96 ± 4,49	0,63
Hemoglobin – 24 months	132,92 ± 3,00	132,22 ± 3,45	0,88
Iron – 6 months	16,74 ± 2,11	18,18 ± 1,48	0,60
Iron – 12 months	21,99 ± 2,42	18,29 ± 1,47	0,26
Iron – 24 months	21,39 ± 1,64	22,71 ± 1,38	0,58
Transferrine % – 6 mo.	22,87 ± 7,16	30,25 ± 3,37	0,31
Transferrine % – 12 mo.	29,87 ± 4,35	30,52 ± 3,64	0,91
Transferrine % – 24 mo.	29,00 ± 2,59	33,45 ± 3,73	0,32
Transferrine – 6 months	2,81 ± 0,19	2,66 ± 0,20	0,60
Transferrine – 12 months	3,00 ± 0,19	2,72 ± 0,20	0,34
Transferrine – 24 months	3,20 ± 0,15	2,95 ± 0,15	0,29
IgA – 6 months	3,29 ± 0,52	2,55 ± 0,33	0,29
IgA – 12 months	3,08 ± 0,52	2,53 ± 0,35	0,44
IgA – 24 months	3,75 ± 0,43	2,20 ± 0,28	0,01
IgG – 6 months	12,05 ± 0,99	10,40 ± 0,41	0,18
IgG – 12 months	10,81 ± 0,87	10,18 ± 0,56	0,60
IgG – 24 months	11,90 ± 0,80	10,71 ± 0,47	0,28
IgM – 6 months	1,03 ± 0,12	0,98 ± 0,15	0,82
IgM – 12 months	1,35 ± 0,24	1,03 ± 0,18	0,35
IgM – 24 months	1,55 ± 0,24	1,23 ± 0,19	0,37
OPNI – 6 months	53,27 ± 1,39	55,78 ± 2,93	0,41
OPNI – 12 months	54,79 ± 1,54	55,67 ± 1,86	0,71

OPNI – 24 months	54,90 ± 1,42	56,41 ± 1,66	0,50
GIQLI – 6 months	97,33 ± 4,29	91,11 ± 8,32	0,47
GIQLI – 12 months	106,00 ± 4,04	95,40 ± 6,81	0,16
GIQLI – 24 months	101,45 ± 5,73	101,78 ± 6,45	0,97
SSBP – 6 months	0,35 ± 0,08	0,33 ± 0,09	0,88
SSBP – 12 months	0,50 ± 0,10	0,28 ± 0,11	0,16
SSBP – 24 months	0,58 ± 0,12	0,39 ± 0,11	0,31
Lipiodol – 6 months	2,66 ± 0,16	3,23 ± 0,26	0,07
Lipiodol – 12 months	2,87 ± 0,19	3,45 ± 0,45	0,17
Lipiodol – 24 months	3,19 ± 0,38	3,75 ± 0,17	0,35
Xylose – 6 months	1072 ± 205	639 ± 112	0,11
Xylose – 12 months	1204 ± 185	905 ± 107	0,21
Xylose – 24 months	1257 ± 154	864 ± 111	0,06
No of meals – 6 months	4,88 ± 0,23	5,64 ± 0,15	0,02
No of meals – 12 months	5,13 ± 0,27	5,38 ± 0,26	0,57
No of meals – 24 months	5,25 ± 0,25	4,86 ± 0,34	0,36

Transferrin %: transferrin saturation in percentage, No of meals: number of meals per day

Nutritional and immunologic laboratory measurements: Most of the measured nutritional parameters followed similar pattern in the two groups, no significant difference were found in regard of serum triglyceride, cholesterol, haemoglobin, iron, transferrine and OPNI between the two groups (table 13). However serum albumin was consequently, significantly higher in patients with an oral pouch at 6, 12 as well as 24 months follow-up (table 13, figure 21). On the other hand serum protein was significantly higher in aboral pouch group at 6 months and serum immunoglobulin-A was significantly higher also in aboral pouch patients at 24 months (figure 20, 22).

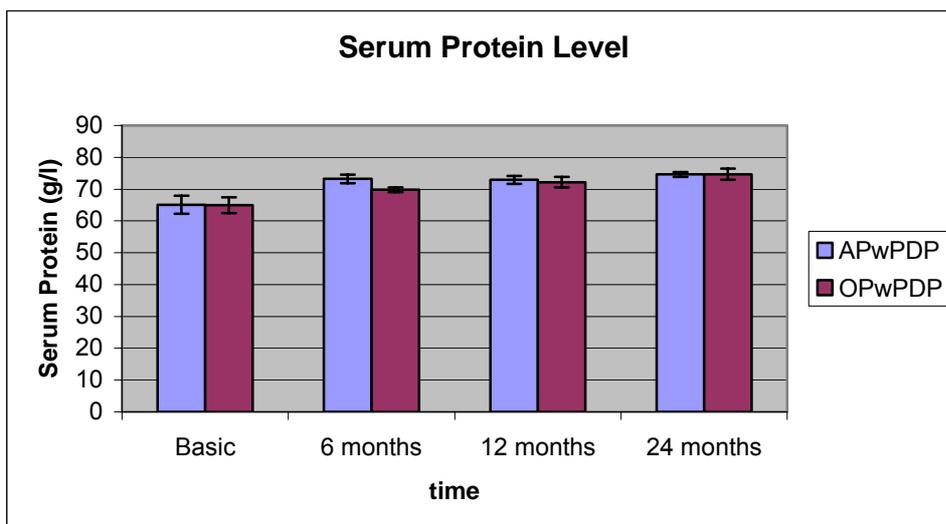


Figure 20: Results serum protein measurements

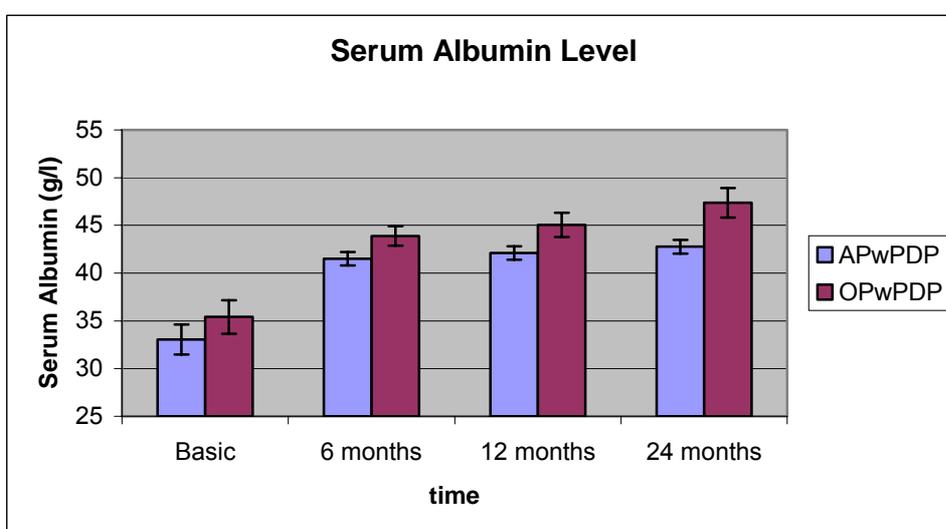


Figure 21: Results of serum albumin measurements

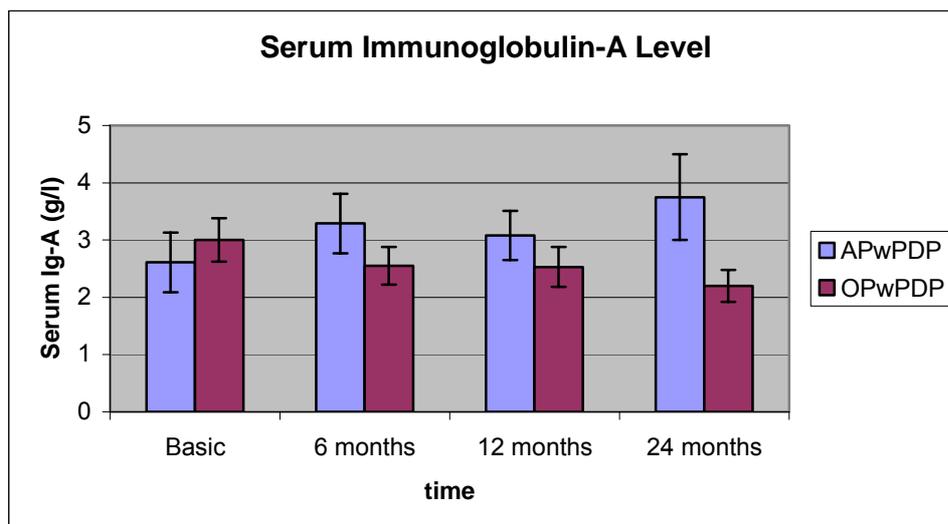


Figure 22: Results of serum immunoglobulin-A measurements

Scintigraphic small bowel passage study (SSBP): No significant difference has been demonstrated regarding the emptying rate of technecium-labelled test meal during small bowel passage scintigraphy between the two groups.

Lipid and carbohydrate absorption tests: There was a tendency toward better lipid absorption - tested by Lipiodol study - in oral pouch patients at 6 months, but is disappeared by 12 months (table 13). And there was a tendency towards better carbohydrate absorption – measured by Xylose test - in aboral pouch patients, which appeared after 6 months and almost reached significant difference by 24 months (table 13). Nevertheless no significant difference has been demonstrated by absorption studies between APwPDP and OPwPDP groups.

Quality of Life: The quality of life –tested by Eypash’s GIQLI – was similar in both groups, slightly growing by time, but no difference has been observed between groups (table 13, figure 23).

The number of meals taken per day differed significantly at 6 months in favour of aboral pouch, but the difference disappeared by time (table 13, fig 24)

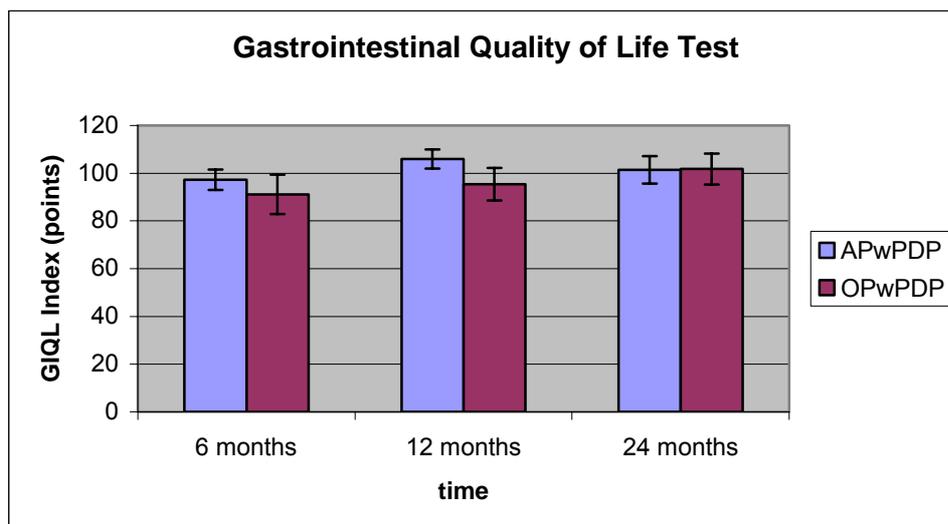


Figure 23: Results of quality of life measurements



Figure 24: Number of meals taken per day

6.2. Discussion

Trial-III comparing Aboral or Oral Pouch, both with preserved duodenal passage, did not find any significant difference between the two groups regarding the primary endpoints, i.e. body weight and quality of life has not been affected by the position of the pouch during reconstruction after total gastrectomy.

Regarding the secondary endpoints some differences have been revealed. The serum level of albumin was higher in Oral Pouch patients

at 6, 12 as well as 24 months postoperatively. It is difficult to find a clear cut explanation for this, especially in the light of the fact, that serum protein levels were higher in the Aboral Pouch group although only at 6 months, while serum Immunoglobulin-A levels were also higher in Aboral Pouch group but at 24 months postoperatively. Thus these higher albumin levels are not reflecting a better protein metabolism in Oral Pouch patients, in general. Serum protein and albumin – as some of the most well known nutritional laboratory measures – have been examined in some studies (51, 61), but found to be affected in only few (51). Nakane et al found a significantly higher protein level in patients with an Oral Pouch with duodenal exclusion reconstruction compared to Roux-en-Y 12 and 24 but not 6 months after surgery (51). They measured serum albumin too, and found no difference in albumin levels comparing Oral Pouch with duodenal exclusion, Oral Pouch with duodenal preservation and Roux-en-Y. In another trial, when they compared Oral Pouch with duodenal passage preservation and Oral Pouch without duodenal passage preservation no difference were found even in serum protein levels (66).

A significant difference was found in favour of Aboral Pouch in the number of meals taken per day, but only at 6 months and then it equalised and even became better in Oral Pouch patients at 24 months though not significantly.

The rest of the measured parameters – serum cholesterol, triglycerid, haemoglobin, iron, transferrine saturation, transferrine, OPNI, SSBP, lipid and carbohydrate absorption tests did not differ significantly between Oral and Aboral Pouch patients.

In summary, the site of the reservoir when added to a duodenal passage preserving reconstruction did not result in any major difference in the examined parameters in the first two years after surgery.

III. GASTROINTESTINAL HORMONE PRODUCTION IS DIFFERENT ACCORDING TO RECONSTRUCTION TYPE AFTER TOTAL GASTRECTOMY (TRIAL-IV)

The background of weight loss after total gastrectomy has long been a matter of examination (75, 76). Though maldigestion and malabsorption of protein and fat resulting in steatorrhea is consistently reported (8, 14, 75, 76, 77) patients after total gastrectomy are able to keep in positive nitrogen balance (14, 76). In an elegant experiment Bradley III et al showed that gastrectomized patients are physiologically capable of caloric intake sufficient to result in weight gain during an in hospital smorgasbord diet, while an accurate record was kept of their ad libitum intake. The same patients reached only 85% of recommended daily caloric allowances for the maintenance of ideal body weight after returning to their home environment. In view of the more than adequate caloric intake during hospitalization neither limited capacity, nor fear of dumping are acceptable explanations. Lack of appetite, absence of hunger sensation, lack of personal initiative or psychical disturbances could contribute to reduced intake, the authors concluded (14).

The physiology of appetite and eating behaviour has drawn increasing attention in the last decades. A number of peripheral and central markers involved in satiety and satiation have been investigated in healthy or obese, young or aged patients (12). Such investigations on gastrectomised subjects are limited in number and yielded inconsistent results.

In Trial-IV the most well studied cholecystokinin, known to cause early satiety, insulin, examined in the long term regulation of food intake, and somatostatin, involved in controversial roles in appetite of healthy individuals (12), but inevitably having a role in dumping syndrome (21), are examined in patients recruited from Trial-II.

1. Clinical Experiment on a Prospectively Randomised Patient Population to Evaluate Postprandial Glucose, Insulin, Cholecystokinin and Somatostatin response in patients after Total Gastrectomy and Aboral Pouch with Preserved Duodenal Passage, Aboral Pouch or Roux-en-Y Reconstruction (Trial IV.)

1.1. Objectives, Eligibility

The aim of Trial-IV is to determine postprandial blood glucose curve, serum insulin, cholecystokinin and somatostatin response in gastrectomised patients after Aboral Pouch, Aboral Pouch with Preserved Duodenal Passage and simple Roux-en-Y reconstruction, compared to each other and to control healthy volunteers.

Eligibility criteria were the same as detailed in section II.1.3. In practice, patients who participated in Trial-II were eligible, if they gave the separate consent to this additional experiment.

1.2. Patients

Patients from the randomised patient population of Trial-II - comparing Aboral Pouch (AP), Aboral Pouch with Preserved Duodenal Passage (APwPDP) and simple Roux-en-Y (RY) reconstructions - were recruited for gastrointestinal hormone measurements, between year 1999 and 2001 (78,79).

Eleven patients with AP, ten with APwPDP and seven with RY reconstruction gave their consents to hormone stimulation test. Six healthy volunteers served as a control group. The average age of the patients was 56,32 years, male to female ratio 19/15. Mean time elapsed after surgery was 16,54 months. Patients' characteristics are shown in table 14. The three patient groups were homogenous with regard to age, gender, stage of disease and post surgical time. All but two patients were operated on for gastric adenocarcinoma, one patient in AP group with gastrointestinal stromal tumor and one with a fibrosarcoma of the stomach. These two patients' disease stages are not shown in table 14.

Table 14: Patients' characteristics

	AP	APwPDP	RY	Normal	p-value
Age (years)	54,27±2,6	58,8±5,1	62,43±2,8	48,83±7,1	0,264
Male:Female	6:5	5:5	4:3	4:2	0,935
Stage I/II/III	2/2/5	2/5/3	1/2/3	NA	0,704
Time after surgery (months)	19,18±3,4	12,30±2,0	18,43±4,7	NA	0,283

NA: not applicable

1.3. Methods of Assessment

Hormone provocation test

After an overnight fast (12-15 hours) a liquid test meal (500 kcal; 70 g carbohydrate, 36 g protein, 7 g fat) was administered at room temperature, in a sitting position. Blood samples were taken 5 minutes before, and 15, 30 and 60 minutes after ingestion of the test meal. One sample from each patient at each time was sent for blood glucose analysis using the glucose oxidase method. Other sample, mixed with EDTA and aprotinin, was collected on ice, centrifuged at 4 °C and the plasma stored at -30 °C for later hormone analysis.

Radioimmunoassays for cholecystikin, insulin and somatostatin

Plasma cholecystikin concentration was measured by a commercial cholecystikin radioimmunoassay kit RK-069-04 (Phoenix Pharmaceuticals Inc Belmont USA). The cholecystikin antibody was raised against CCK octapeptide 26-33 (non-sulfated). The sensitivity of the assay was 1 pg/tube. The CD50 for the calibration curve was 35,44 pg/tube.

Plasma insulin concentration was measured by a commercial insulin radioimmunoassay kit RK-400M (Institute of Isotopes Budapest Hungary). The insulin antibody was highly specific for human insulin with cross-reactivity to human proinsulin of 65%. The sensitivity of the

radioimmunoassay was 5 μ IU/ml, the inter-assay variance 6,2%, the intra-assay variance was 7,1%.

Plasma somatostatin was measured by a specific and sensitive radioimmunoassay developed at the Department of Pharmacology and Pharmacotherapy, University of Pécs (80).

1.4. Statistics

Experimental design was approved by the University of Pécs Ethics Committee. All patients and healthy volunteers gave informed consent to the experiment. SPSS 11.5 software was applied to compare data. Statistical significance was analysed by factorial analysis of variance (ANOVA) for the series of hormone values in time and one way ANOVA for integrated secretions. Integrated secretions were calculated as the area under the hormone concentration curve. Parametric variables of patient characteristics were compared with one way ANOVA, while for nonparametric variables the Kruskal-Wallis test was used. Results are expressed as mean \pm SEM. Differences with a p value $< 0,05$ were considered significant, p-value is represented in most comparisons.

1.5. Results

Glucose

Figure 25 demonstrates the blood glucose levels in the four groups during meal provocation test. Glucose curve for controls seems flat, while for the operated patients reach higher values. The curves look diabetoid, most prominently in RY patients. Factorial analysis of variance found significant difference between the curves for the four groups. Groups with duodenal exclusion (RY and AP) had significantly higher glucose levels compared to the normal control group.

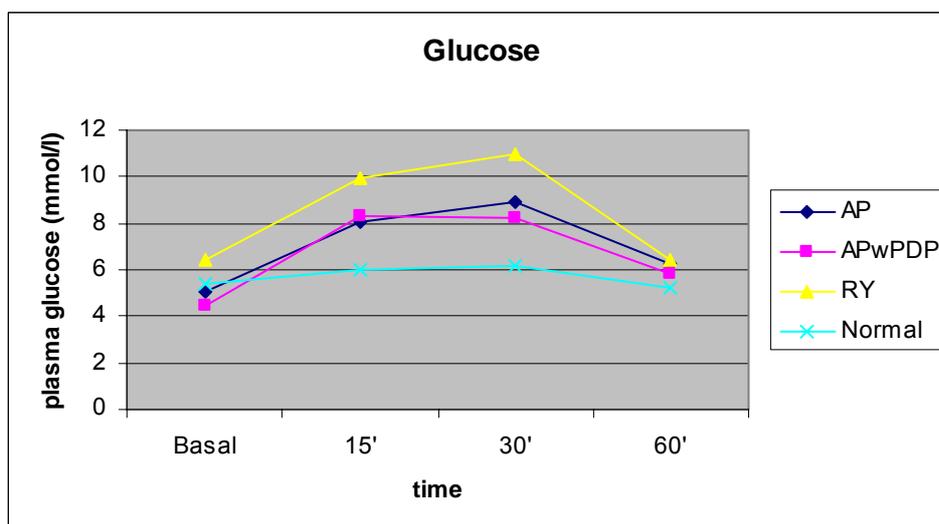
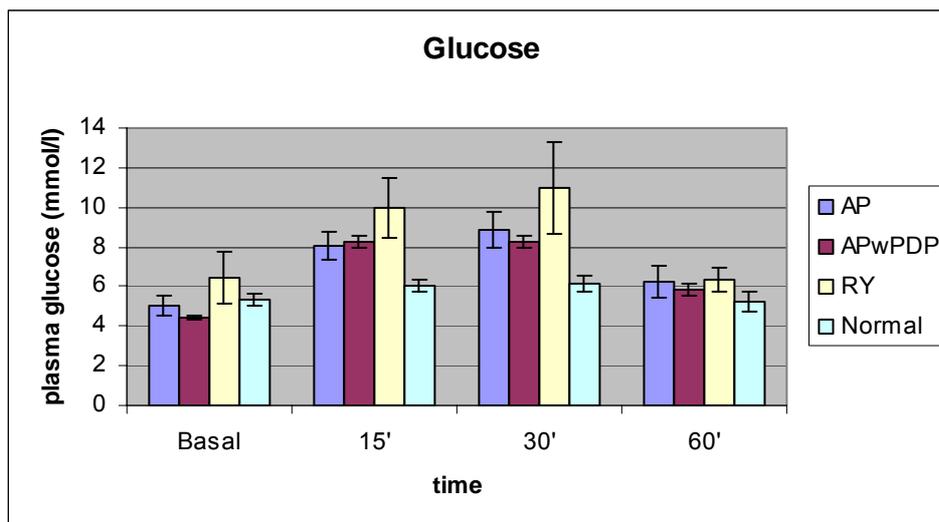


Figure 25: Basal and stimulated plasma glucose levels in RY, AP and APwPDP patients and in normal controls. Curves differed significantly by factorial ANOVA $p=0,002$. Post hoc test showed RY vs normal $p=0,025$, RY vs AP $p=0,044$

Insulin

The insulin level increased to abnormally high values in all three gastrectomised groups in response to food stimulus, compared to healthy control (figure 26). The basal values did not differ between the four groups. The insulin curve ran highest in patients with preserved duodenal passage (APwPDP). Factorial ANOVA showed that the curves differed significantly according to the type of the groups. Post

hoc comparisons showed significant difference between normal and AP and normal versus APwPDP groups (figure 26). The integrated secretion was higher in the operated groups than in controls, however the difference did not reach a significant level, probably because of the high standard deviation of insulin data (table 15).

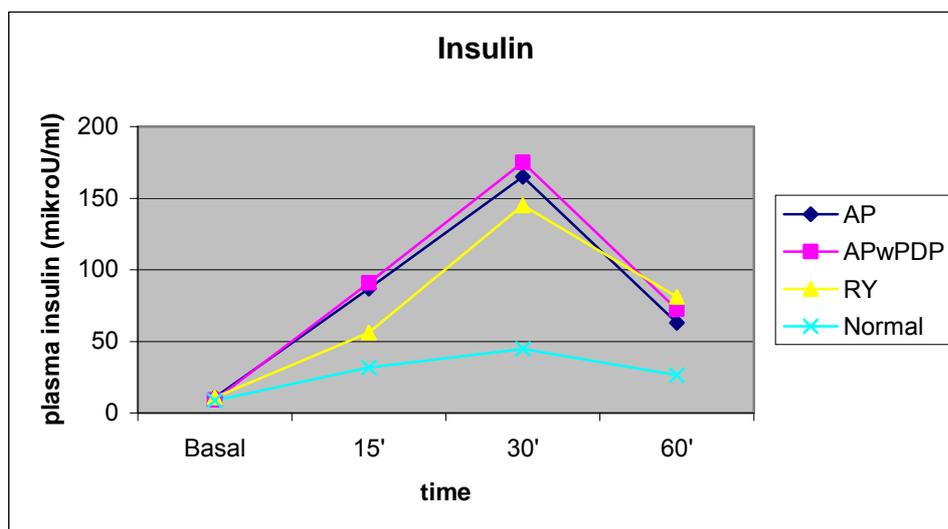
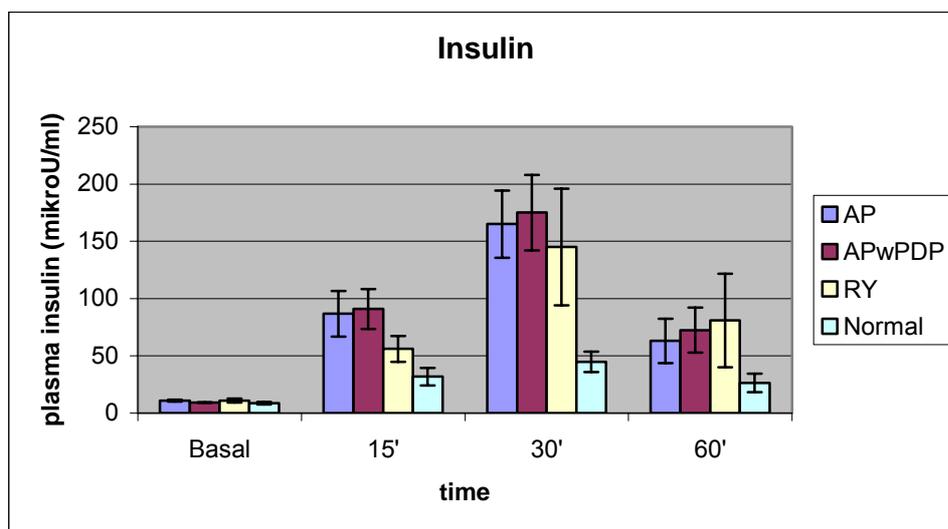


Figure 26: Basal and stimulated plasma insulin levels in RY, AP and APwPDP patients and in normal controls. Curves differed significantly by factorial ANOVA $p=0,005$. Post hoc test showed normal vs AP $p=0,002$, normal vs APwPDP $p=0,001$.

Table 15: Integrated secretion of insulin, cholecystokinin (CCK) and somatostatin in patients with RY, AP and APwPDP reconstruction and in normal controls

	Insulin ($\mu\text{U/ml} \times 60 \text{ min}$)	CCK ($\text{pg/ml} \times 60 \text{ min}$)	Somatostatin ($\text{fmol/ml} \times 60 \text{ min}$)
AP	6046,50 \pm 968,26	1450,83 \pm 85,65 [*]	827,454 \pm 106,13 ^{S†}
APwPDP	6459,97 \pm 1206,43	875,25 \pm 77,81 [∞]	541,50 \pm 38,57 [†]
RY	5407,17 \pm 1894,78	1337,75 \pm 85,81 ^{‡∞}	666,10 \pm 123,24
Normal	1954,62 \pm 379,85	678,75 \pm 36,65 ^{‡*}	436,37 \pm 24,71 [§]
p-value ANOVA	0,105	0,0001	0,024

Post hoc multiple comparisons: ‡Normal vs RY p=0,0001, *Normal vs AP p=0,0001, ∞RY vs APwPDP p=0,004, §Normal vs AP p=0,006, †APwPDP vs AP p=0,017

Cholecystokinin

Figure 27 demonstrates cholecystokinin levels in response to test meal. Regarding this gastrointestinal hormone the examined groups separated to a group with higher basal as well as stimulated values, incorporating patients with duodenal exclusion (RY and AP patients) and to a group of lower values, including APwPDP patients and the healthy controls (figure 27). ANOVA analysis showed significant difference between the curves according to reconstruction type. Post hoc comparisons showed that all four groups differed significantly from each other except AP from RY. For integrated cholecystokinin secretion RY and AP groups showed significantly higher amount of secretion compared to normal, while data for APwPDP did not differ from normal significantly (table 15).

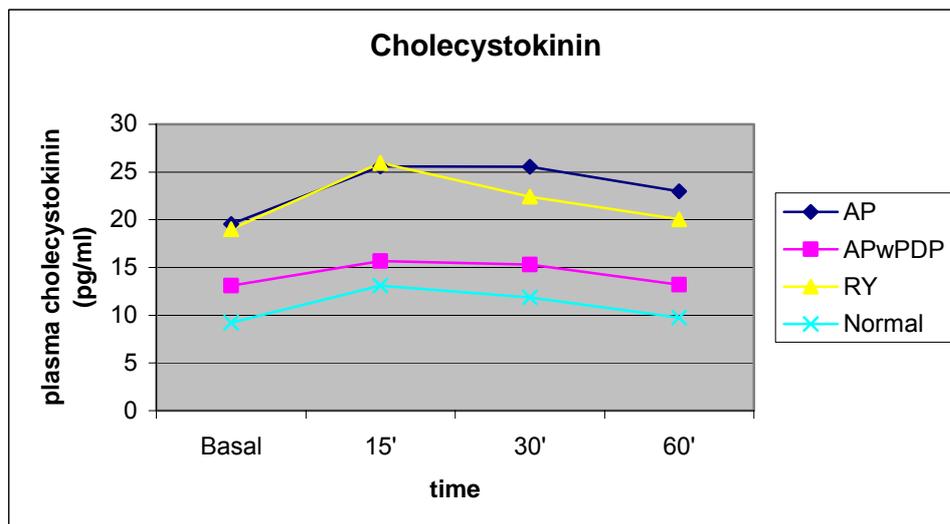
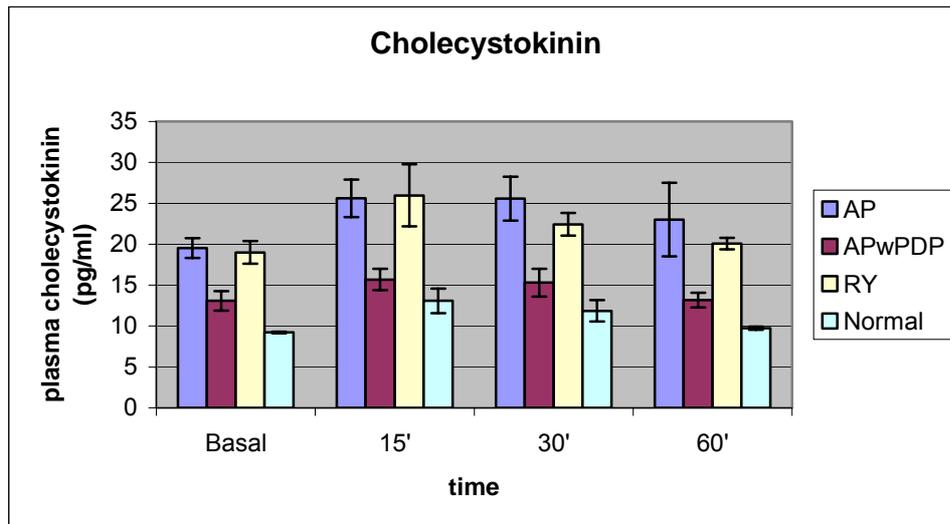


Figure 27: Basal and stimulated plasma cholecystinin levels in RY, AP and APwPDP patients and in normal controls.

Curves differed significantly by factorial ANOVA $p < 0,001$. Post hoc test showed normal vs RY $p < 0,001$, normal vs AP $p < 0,001$, normal vs APwPDP $p = 0,003$, RY vs APwPDP $p < 0,001$, AP vs APwPDP $p < 0,001$.

Somatostatin

The postprandial curves for somatostatin plasma levels (fig 28) differed even in shape between the groups. The control group reached peak value around 15 minutes and somatostatin level decreased from that point. In patients with duodenal exclusion (RY and AP) somatostatin level increased longer and further, almost twice as high as in normal controls, until around 30 minutes postprandially, than seemed to reach a plateau in AP patients, while start to decrease in RY. In patients with APwPDP reconstruction the peak and plateau were at the same time like in AP group, however somatostatin level did not reach much higher values than in control patients. The data sets differed significantly regarding type of operation analyzed by factorial ANOVA. Post hoc tests showed significantly higher values for AP compared to normal and for AP compared to APwPDP, the rest of the groups did not differ significantly from each other. The integrated secretions also differed significantly with higher values for AP and lower for APwPDP and normal control groups (table 15). Postprandial curve for RY group ran between the curves of AP and APwPDP, integrated secretion of somatostatin for RY patients were also between this two groups' results, but there were no significant difference of RY data from any other groups most likely because of the high standard deviation in this group.

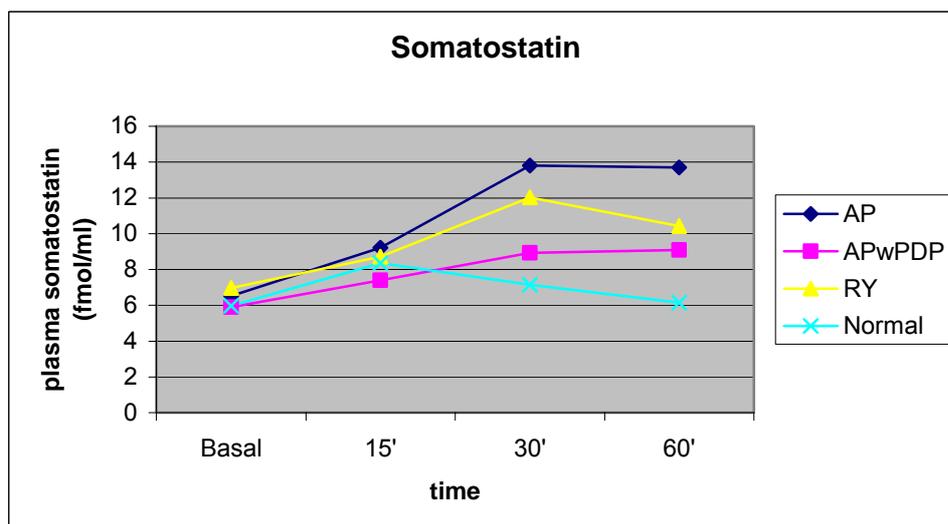
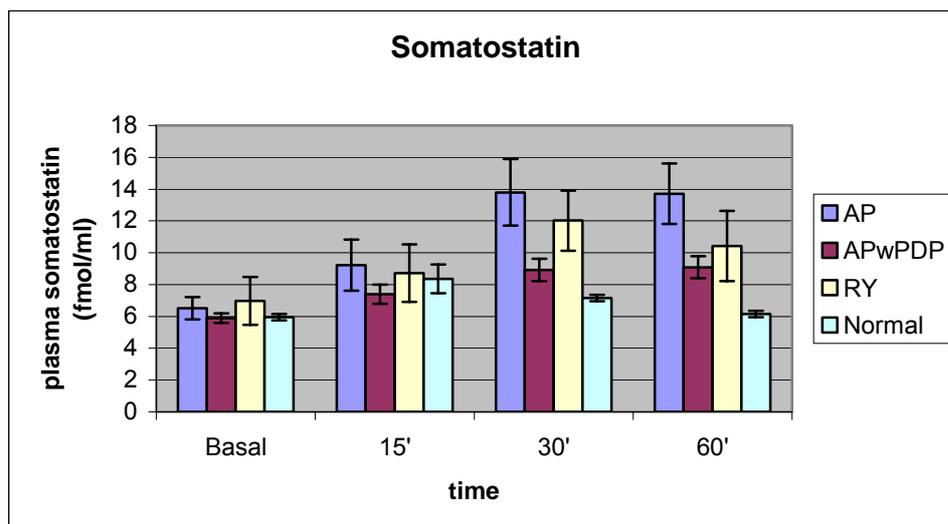


Figure 28: Basal and stimulated plasma somatostatin levels in RY, AP and APwPDP patients and in normal controls.

Curves differed significantly by factorial ANOVA $p=0,001$. Post hoc test showed normal vs AP $p=0,001$, AP vs APwPDP $p=0,027$.

1.6. Discussion

From a medline search for gastrointestinal hormone measurements in patients undergone gastric surgery no clear-cut conclusion could be drawn regarding basal and stimulated levels of the above measured hormones. Different studies measured endogenous production of hormones in response to either liquid or solid test meal, or to intraduodenal administration of nutrients. Others administered the hormones exogenously in a fasting or postprandial state and examined the reaction. Subjects have undergone either total or partial gastric resection, with regard, or regardless of the way of reconstruction or they had limited gastric surgery such as vagotomy, antrectomy or pyloroplasty (8, 9, 15, 53, 77, 81, 83, 84, 85, 86)

Blood sugar regulation has long been described to be disturbed after gastrectomy, with early hyperglycaemia and late hypoglycaemia during oral glucose tolerance test (14). Regarding the type of reconstruction Schwarz et al found significantly higher glucose levels in Roux-en-Y patients and in patients with pouch construction and duodenal exclusion while in case of preservation of the duodenal route the pathologic glucose tolerance did not develop (53). Friess et al though, in patients with total gastrectomy and preserved duodenal passage, found significantly higher glucose levels in the first 45 minutes after a liquid test meal (8). In our study postprandial glucose curves ran significantly higher in patients with duodenal exclusion (RY and AP) compared to controls, supporting the hypothesis that duodenal exclusion disturbs glucose homeostasis more, than reconstructions with a preserved duodenal passage.

In contrast to the diabetoid postprandial glucose curves after gastric resection it has also been described that gastrectomy improves glucose tolerance, ameliorates diabetes mellitus and decreases insulin demands in diabetic patients (81). The elevated insulin levels and increased integrated insulin secretion after a test meal in gastrectomized patients found in the present study agrees well with these clinical observations. Other studies in the literature on subjects after total gastrectomy regarding endogenous insulin production also

found higher postprandial levels (8, 53). Regarding duodenal passage preservation Schwarz et al found the insulin level elevated only in jejunum interposition cases and not in cases, where the duodenum was excluded. In our experiment the postprandial insulin secretion draws an elevated curve for all operated groups regardless of the reconstruction type (Fig 4). Insulin secretion is stimulated by the high blood glucose peak, as a result of the early and fast intestinal absorption of glucose, due to the rapid intestinal transit in gastrectomized state. In addition enteroglucagon or glicentin, GLP-1 and GLP-2 also stimulates insulin release. Enteroglucagon is normally secreted by the distal intestinal mucosa if nutrients – especially glucose - reach as far as this point in the bowel. It stimulates insulin release to improve glucose metabolism. Enteroglucagon has been shown to be secreted by the small bowel at an increased rate after gastrectomy (15).

Cholecystokinin (CCK) has been one of the most investigated gastrointestinal hormones in gastrectomized patients. In our experiment the basal level was found to be raised in all three groups after total gastrectomy. The integrated postprandial secretion though were elevated only in reconstructions with duodenal exclusion (RY and AP), while in APwPDP reconstruction, where the duodenal route was preserved, the integrated postprandial secretion did not differ significantly from control.

Clinical studies investigating CCK secretion in patients after total gastrectomy (8, 53, 77, 82, 83, 84, 85) found an equal or higher basal level of the hormone in gastrectomized patients compared to healthy controls. The postprandial level after gastrectomy was higher in most studies compared to normal (8, 53, 77, 84, 85), but lower in two (82, 83). Some studies also calculated the integrated postprandial CCK secretion. It was found to be higher after total gastrectomy in two experiments (53, 77) and equal to normal in one (85). In those studies though, where CCK production in gastrectomized subjects were found to be the same or less inducible than in normal controls, a solid test meal was applied, or fat load was given directly intraduodenally. CCK, by relaxing the fundus and increasing pyloric tone, has a well

established role in delaying gastric emptying (9), in this context regulating its own release by a short circuit feed back mechanism. Nutrients entering the duodenum release CCK, which in turn inhibits gastric emptying. Consequently, nutrient flow ceases and CCK secretion decreases. If patients after total gastric resection are compared to healthy people, the difference is that operated patients do not have the target organ for this effect of CCK, therefore CCK level remains elevated. The food, entering the duodenum brings about CCK secretion, but there is no way for CCK to stop nutrient flow, which results in a higher CCK level. Experiments with a setting of intraduodenal administration of test food can show the differences more precisely in CCK producing capacity between healthy and operated subjects, i.e. cholecystokinin levels raise more slowly but the overall integrated production is equal to normal (83, 86). The obtained results though will not reflect everyday situation nor will help to reveal the background of decreased initiative of gastrectomized patients to eat.

In our study different reconstruction types were compared after total gastrectomy to examine the significance of duodenal exclusion or preservation and pouch construction. Of the above cited experiments Schwarz et al examined CCK secretion in response to a 400 kcal liquid test meal in patients after total gastrectomy with Roux-en-Y reconstruction, with a 10 or a 20 cm long oral pouch and Roux-en-Y reconstruction and with jejunum interposition and either 10 or 20 cm long oral pouches. The peak concentrations of CCK, as well as the integrated postprandial CCK secretions were significantly higher in all operated groups compared to healthy controls, but there were no significant differences between the operated groups (53). In the present study patients after total gastrectomy with preserved duodenal passage had about the same postprandial secretions than normal, but patients with duodenal exclusion (RY and AP) had significantly higher postprandial CCK production.

The disturbed feed back of gastric emptying on CCK secretion can explain higher CCK levels after gastrectomy in general, but the normal levels in case of duodenal passage preservation must have a

different explanation. The exocrine pancreatic function is described to be insufficient after gastrectomy (8), maybe partly because of the vagal denervation of the pancreas (86), but more importantly because of a pancreatico-cibal asynchrony (14), i. e. a disturbed speed and order of food passage and endocrine and exocrine secretions along the gut. There is a feed back regulation of pancreatic secretion by intraluminal proteases described in humans (89). The same feed back is certainly mediated by CCK in dogs, but in humans the role of CCK is less clear, rather seems to act together with the cholinergic system as a neuromodulator (90). If this feed back operates, at least partly, with CCK in humans, the exocrine pancreatic insufficiency (8), caused by the pancreatico-cibal asynchrony, may also add to the elevated level of CCK in case of duodenal exclusion, and might explain the normal levels when duodenal passage is preserved. This is supported by our earlier finding of a significantly better lipid absorption, measured by the Lipiodol test in patients with preserved duodenal passage (APwPDP) compared to Roux-en-Y (79).

CCK has extensively been examined in connection with appetite and satiety (12). Experiments on healthy individuals proved a dose dependent suppressing effect of CCK on appetite (13). Studies with young and elderly healthy individuals revealed an elevated basal and postprandial level of CCK in the elderly, probably as a reason for the observed reduced food intake in this group (87). This so called anorexia of aging, is accompanied by a slowing of gastric emptying, which can also be attributable to the higher CCK level. Our results of a more physiologic CCK response in reconstruction preserving the duodenal route support the application of duodenal passage preservation for postgastrectomy reconstruction, to avoid the probable satiating effect of CCK. This probable difference in appetite did not result in higher body weight in patients with duodenal passage preservation, as reported in our randomized trial, however may contribute to the better quality of life found in this group in the first postoperative years (79). Although the direct effect of CCK on appetite in gastrectomized subjects - where

gastric fullness cannot attribute to the CCK's effect to reach satiety (88) - remains to be elucidated.

Somatostatin in connection with gastrectomy was mainly examined as a potential cure for dumping syndrome (21, 91). Given exogenously, somatostatin – or its long acting analogue octreotide - proved to be able to alleviate symptoms of dumping, reduce pulse rate and abolish late hypoglycaemia. However in chronic use intractable abdominal cramps, and diarrhoea can develop (92), the inhibition of insulin release by somatostatin leads to hyperglycaemia and diabetes (93), and the inhibition of pancreatic exocrine secretion may worsen malabsorption and dumping (92). Those few studies which examined endogenous production of somatostatin, revealed that patients who are doing well after gastrectomy tends to have higher basal levels of this hormone, while those, who have dumping symptoms and manometric proof of abnormal bowel motility, have lower levels of somatostatin (94). No study has examined endogenous somatostatin production in response to test meal in gastrectomised patients before. In our study somatostatin levels in patients after gastrectomy were not different from normal in the fasting state. In the first 15 minutes it raised slightly in all four groups. Afterwards it returned to basal level in healthy controls, remained slightly raised in patients with preserved duodenal passage, while increased in cases of duodenal exclusion. Sixty minutes were not enough to detect it return to basal level in the operated groups, but certainly it raised significantly higher in patients with duodenal exclusion (RY and AP) Secretion of somatostatin is stimulated by most of the factors which stimulates insulin production, such as enteral glucose and aminoacid load. Cholecystokinin as well as insulin also increases somatostatin secretion. In response somatostatin acts as a generally inhibiting gastrointestinal hormone, decreasing the secretion of most gastrointestinal hormones. Thus the observed differences between normal and duodenal exclusion patients may only represent a response to the higher levels of other hormones such as insulin and cholecystokinin in patients with duodenal exclusion. The significantly

slower transit of APwPDP reconstruction demonstrated in Trial-II can give a possible explanation to this difference in somatostatin release.

The whole problem of postgastrectomy symptoms might be attributed to the accelerated intestinal transit. The rapid transit results in accelerated glucose absorption bringing about higher output of insulin. Accelerated transport of peptides and lipids gives an abnormally large stimulus to cholecystokinin production, magnified by the brake in the feed back regulation. All ends in abnormally high gastrointestinal hormone levels, which brings about increased production of somatostatin. And somatostatin will arrest, as needed, this cascade of GI hormone production, but additionally reduces gut motility and digestive juice production. The whole phenomenon probably becomes less significant with time due to the intestinal adaptation (85). This hypothesis though needs further evaluation.

In summary our experiment supports a diabetoid blood glucose profile in the first postprandial hour in patients after gastrectomy and routine Roux-en-Y reconstruction, with higher insulin concentrations, elevated cholecystokinin levels and an increasing somatostatin release after 15-30 minutes postprandially. The creation of a pouch seems not to improve much on this disturbed regulation. Duodenal passage preservation however helps to moderate the postprandial cholecystokinin elevation and results in a less steep postprandial plasma somatostatin curve, probably reflecting a decreased need for arresting the abnormally high output of other gastrointestinal hormones in these patients.

Our earlier data proved better quality of life in the first postoperative year for AP compared to RY patients, and for APwPDP compared to both AP and RY (79). Long term data have not been reported yet. This better life quality may at least partly come from the differences in gastrointestinal hormone profile.

Whether these differences in gastrointestinal hormone production in favour of duodenal passage preservation result in less compromise in appetite and hunger sensation and are able to contribute to a less reduced caloric intake in patients after gastrectomy, needs

further evaluation. Furthermore, recently discovered hormones involved in appetite and meal size regulation, such as ghrelin and leptins needs to be examined in gastrectomized patients.

IV. NEW FINDINGS

- 1) Two conceptionally new reconstruction methods – the Aboral Pouch and the Aboral Pouch with Preserved Duodenal Passage - were introduced and examined under the rules of prospective randomised trials, comparing them to the today gold standard Roux-en-Y reconstruction after total gastrectomy.
- 2) Aboral Pouch and Aboral Pouch with Preserved Duodenal Passage proved to be feasible reconstruction methods after total gastrectomy, i.e. they can be performed at the same mortality and morbidity rate than the standard Roux-en-Y reconstruction.
- 3) According to the primary outcome measures, no difference in postoperative development in body weight has been revealed among the different reconstruction types while Aboral Pouch with Preserved Duodenal Passage proved to provide a better quality of life in the first year after surgery.
- 4) According to the secondary outcome measures Aboral Pouch itself proved to provide some advantages in iron and lipid metabolism in the short term (higher iron level at 6 months, higher cholesterol level, transferrine saturation and lipid absorption at 12 months) and in reservoir capacity in the short and long term (lower number of meals taken per day at 12 months and long term).
- 5) Secondary outcome measures regarding Aboral Pouch with Duodenal Passage Preservation provided even more improvement in iron and lipid metabolism in the short term (higher iron level at 6 and 12 months and transferrine saturation at 12 months, higher cholesterol level and better lipid absorption at 12 months) furthermore a more favourable dynamics of transit was proven in the short and long term (slower transit on SSBP at

6 and 24 months and in the long term) and the reservoir capacity was equally improved as for Aboral Pouch only.

- 6) The site of the pouch – whether it is placed orally or aborally – does not seem to be important, as no major difference has been found between APwPDP and OPwPDP reconstructions.
- 7) In the gastrointestinal hormone regulation major differences were discovered according to the different reconstruction types after total gastrectomy. The preservation of the duodenal passage was shown to ensure a more physiologic production of cholecystikinin, which might have a very important role in the regulation of hunger and appetite in patients, undergone total gastrectomy.
- 8) Somatostatin release also was proven to be dependent on the preservation of the duodenal passage, which provided a slower and less pronounced increase of the hormone level reflecting probably a lower need for breaking the uncontrolled production of other gastrointestinal hormones, i.e. a lesser tendency toward dumping and other postgastrectomy disturbances.

In summary two new types of postgastrectomy reconstruction procedures were introduced and examined. Trials I-III showed, that preservation of the duodenal passage provides several, well established advantages over the standard simple Roux-en-Y reconstruction, which altogether results in a better quality of life in the first postoperative year. The construction of a pouch itself gives also some, less pronounced advantages, independent of the site of the reservoir. In the long term, probably because of intestinal adaptation, little differences remain, but the slower passage provided by preserved duodenal passage is a considerable advantage.

Trial IV revealed that from the viewpoint of gastrointestinal hormone production, more physiological cholecystikinin and somatostatin

responses are seen in reconstruction with preserved duodenal passage, which may give an explanation to the above findings and draw scientific attention to the complex hormonal and neural consequences of a simple removal of an organ and reorganisation of the gastrointestinal route.

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Am J Surg 2003; 185: 354-359.

VII. Publications

1. Presentations

1.1. In connection with Thesis:

1. **K Kalmár**, L Cseke, T Beró, OP Horváth: A new method for the construction of a gastric pouch after total gastrectomy (előadás)
Magyar Gastroenterológiai Társaság 40. Nagygyűlése, Balatonaliga, 1998.
2. **Kalmár K**, Cseke L, Beró T, Horváth ÖP: Új típusú pótyomor képzése total gastrectomia után (előadás)
A Magyar Sebész Társaság 54. Nagygyűlése, Budapest 1998.
3. **K Kalmár**, L Cseke, ÖP Horváth: A new method for the construction of a gastric pouch after total gastrectomy (video)
3rd International Gastric Cancer Congress, Seoul, Korea, 27-30 April, 1999.
4. **K Kalmár**, L Cseke, ÖP Horváth: Prospective randomized study to evaluate nutritional consequences of pouch construction after total gastrectomy (poszter)
Magyar Gastroenterológiai Társaság 41. Nagygyűlése, Balatonaliga, 1999.
5. **K Kalmár**, L Cseke, ÖP Horváth: Comparing quality of life and nutritional parameters after total gastrectomy and a new type of pouch construction with simple Roux-en-Y reconstruction (előadás)
38th World Congress of Surgery of the ISS, ISW99 Vienna, Austria, August 15-20, 1999.

6. **Kalmár K**, Cseke L, Horváth ÖP: Aborális pouch - egy új típusú pótyomor képzése total gastrectomia után (előadás)
XVII. Magyar Kísérletes Sebészeti Kongresszus, Szeged, 1999.
7. **Kalmár K**, Cseke L, Horváth ÖP: Aborális pouch képzés
nutricionális következményei totális gastrectomia után:
prospektív, randomizált tanulmány (előadás)
Magyar Mesterséges Táplálási Társaság Kongresszusa,
Kecskemét, 1999.
8. **K Kalmár**, L Cseke, ÖP Horváth, K Zámbó, J Hadjiev:
Nutritional advantages of aboral pouch construction after total
gastrectomy (előadás)
10th Congress of the ESSO, Gröningen, 2000.
9. **K Kalmár**, L Cseke, ÖP Horváth: Aboral pouch with
preserved duodenal passage - a new type of gastric
substitute after total gastrectomy (poszter)
10th Congress of the ESSO, Gröningen 2000.
10. ÖP Horváth, **K Kalmár**, L Cseke: Prospective, randomized
evaluation of aboral pouch - a new type of gastric substitute -
after total gastrectomy
Deutsche Gesellschaft für Chirurgie, Berlin May 2000.
11. **K Kalmár**, L Cseke, ÖP Horváth: Attempts to optimize
reconstruction after total gastrectomy: aboral pouch with
preserved duodenal passage (előadás)
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