Randomised Comparison of Aboral Pouch with Preserved Duodenal Passage to Oral Pouch with Preserved Duodenal Passage

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 1).

Table 1: Basic anthropometric and laboratory parameters in 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
Triglicerid (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 2, 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.

Table 2: 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 2). However serum albumin was consequently, significantly higher in patients with an oral pouch at 6, 12 as well as 24 months follow-up (table 2). 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.

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 2). 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 2). 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 2).

The number of meals taken per day differed significantly at 6 months in favour of aboral pouch, but the difference disappeared by time (table 2)

Discussion

The comparison of Aboral or Oral Pouch, both with preserved duodenal passage, did not found 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, but found to be affected in only few. 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. 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.

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, triglicerid, 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.

Long Term Results of comparing Aboral Pouch, Aboral Pouch with Preserved Duodenal Passage and simple Roux-en-Y reconstruction

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 3). Patients in APwPDP group gained the most weight, their BMI was 7% higher than postoperatively, but the difference between the groups was not significant.

Table 3: 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
Triglicerid	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, triglicerid, cholesterol, haemoglobin, iron, transferrine saturation, transferrine, immunoglobulins and OPNI – among the three groups (table 3).

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).

Lipid and carbohydrate absorption tests: No reconstruction dependent difference has been detected regarding lipid and carbohydrate absorption in the long term (table 3).

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).

Discussion

Most of the differences seen in comparing these three reconstruction types 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. Ivonen et al reported better quality of life in pouch patients compared to Roux-en-Y 5 years after surgery. 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. 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.

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.

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

Patients

Patients from the randomised patient population 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.

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 4. 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 4.

Table 4: 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

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 ^{0}C and the plasma stored at -30 ^{0}C for later hormone analysis.

Radioimmunoassays for cholecystokinin, insulin and somatostatin

Plasma cholecystokinin concentration was measured by a commercial cholecystokinin radioimmunoassay kit RK-069-04 (Phoenix Pharmaceuticals Inc Belmont USA). The cholecystokinin 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 μIU/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.

Results

Glucose

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.

Insulin

The insulin level increased to abnormally high values in all three gastrectomised groups in response to food stimulus, compared to healthy control. 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. 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.

Cholecystokinin

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. 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.

Somatostatin

The control group for somatostatin reached peak value around 15 minutes and the 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. 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.

Discussion

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. 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. Long term data have not been reported yet. This better life quality may at least partly come from the differences in gastrointestinal hormone profile.

Weather 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.

Examining the Presence of Biliary Reflux at Different Types of Reconstructions after Total Gastrectomy

The manometry and Bilitec biliary reflux studies are still going on. Upper endoscopy, esophageal manometry and 24 hour Bilitec examinations were carried out for two patients with aboral pouch, five with aboral pouch with preserved duodenal passage three with oral pouch with preserved duodenal passage and four with control Roux-en-Y reconstruction. Further four patients are planned to be included before analysis.