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The impact of the repair of staple line dehiscence in post-RYGB patients on glucose homeostasis and gut hormones — a preliminary study

Wpływ chirurgicznego leczenia rozejścia linii szwu mechanicznego u chorych po zabiegu ominięcia żołądka sposobem Roux na gospodarkę węglowodanową oraz stężenia hormonów jelitowych — badanie wstępne

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Abstract

Introduction: Staple-line disruption (SLD) following Roux-en-Y gastric bypass (RYGB) results in weight regain. This study evaluated glucose homeostasis and gut hormonal changes following surgical repair of gastrogastric fistula.

Material and methods: Three patients with SLD underwent an oral 75 g glucose tolerance test (OGTT) before (baseline) and one week after gastric pouch restoration. Plasma glucose, insulin and glucagon glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide–1 (GLP-1) were measured in the OGTT samples. Fasting plasma levels of ghrelin and leptin were assessed.

Results: Restoration of gastric pouch provided moderate amelioration of glucose metabolism and gut hormones, yet without complete normalisation of glucose homeostasis at one week after surgery. Duodenal passage exclusion resulted in early improvement of control fasting plasma glucose with decrease of glucagon from 18.5 to 15 (ng/mL, by 19%), relatively stable insulin and decline of incretin hormones (GIP and GLP-1). Post-challenge measurements confirmed amelioration of glycaemic control with decrease of plasma glucose from 182 to 158 mg/dL at 60 minutes. Surgical re-intervention resulted in exacerbation of GIP response with brisk rise in plasma level, accompanied by considerable increase of peak insulin concentration. The overall post-challenge glucagon and GLP-1 responses were decreased. Marked decrease in fasting plasma ghrelin and leptin were observed.

Conclusions: Our report gives further insight into the hormonal mechanisms underlying the effects of surgically altered anatomy of different parts of the small intestine on glucose homeostasis that is highly important, since it may facilitate novel conservative therapies of diabetes without the need for surgery. **(Endokrynol Pol 2013; 64 (1): 7–12)**

Key words: *Roux-en-Y gastric bypass, staple-line disruption, weight regain, glucose homeostasis*

Streszczenie

Wstęp: Rozejście linii szwu mechanicznego (SLD) po operacji ominięcia żołądka sposobem Roux (RYGB) skutkuje nawrotem otyłości. W badaniu poddano ocenie zmiany gospodarki węglowodanowej oraz stężeń hormonów jelitowych po chirurgicznym leczeniu przetoki żołądkowo-żołądkowej.

Materiały i metody: Trzech chorych z SLD poddano doustnemu testowi obciążenia 75 g glukozy (DTOG) przed oraz jeden tydzień po zabiegu odtworzenia proksymalnego zbiornika żołądkowego. W próbkach krwi pobranych podczas DTOG oceniano osoczowe stężenie glukozy, insuliny, glukagonu, insulinotropowego peptydu zależnego od glukozy (GIP) oraz glukagonopodobnego peptydu 1 (GLP-1). We krwi pobranej na czczo oceniano dodatkowo stężenie greliny oraz leptyny.

Wyniki: Odtworzenie proksymalnego zbiornika żołądkowego prowadzi do umiarkowanej poprawy metabolizmu glukozy oraz stężeń hormonów jelitowych, jednakże bez całkowitej normalizacji homeostazy węglowodanowej w jeden tydzień od zabiegu operacyjnego. Wyłączenie pasażu dwunastniczego skutkowało wczesną poprawą kontroli stężenia glukozy na czczo, ze spadkiem stężenia glukagonu z 18,5 do 15 (ng/ml, o 19%), względnie stałym stężeniem insuliny oraz spadkiem stężeń hormonów inkretynowych (GIP i GLP-1). Pomiary dokonane po obciążeniu glukozą potwierdziły poprawę kontroli glikemii ze spadkiem osoczowego stężenia glukozy z 182 do 158 mg/dl w 60 minucie testu. Zabieg chirurgiczny skutkował nasileniem sekrecji GIP z wyraźnym wzrostem osoczowego stężenia tego hormonu po obciążeniu glukozą, z towarzyszącym znacznym wzrostem najwyższego stężenia insuliny. Całkowite stężenie glukagonu oraz GLP-1 po obciążeniu glukozą malało. Zaobserwowano znaczny spadek stężenia greliny oraz leptyny na czczo.

Wnioski: Praca pozwala na dalsze poznanie mechanizmów hormonalnych leżących u podstaw wpływu chirurgicznie zmienionej anatomii różnych części jelita cienkiego na homeostazę węglowodanową. Poznanie tych mechanizmów jest bardzo istotne z punktu widzenia klinicznego, gdyż w przyszłości może przyczynić się do wprowadzenia nowych metod leczenia zachowawczego cukrzycy, bez konieczności wykonywania operacji bariatrycznych. **(Endokrynol Pol 2013; 64 (1): 7–12)**

Słowa kluczowe: *ominięcie żołądka sposobem Roux, rozejście linii szwu mechanicznego, nawrót otyłości, homeostaza węglowodanowa*

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Introduction

Bariatric surgery has become the therapy of choice for morbid obesity. One of these procedures, Roux-en-Y gastric bypass (RYGB), has been found to be equally effective in achieving substantial and durable weight loss as well as in amelioratingobesity-related co-morbidities including type 2 diabetes mellitus (T2DM) [1, 2] and other concomitant disorders [3]. The remarkable improvement in glucose control is usually linked to the postoperative reduction of body mass. However, this beneficial effect does not depend on weight loss alone [4]. In most patients, hypoglycaemic medications are already not required soon after surgery [5]. The underlying mechanism of this immediate metabolic effect is still unknown.

Several studies have proved that a duodenal switch provides superior resolution of diabetes compared to a gastric bypass. It has been suggested that surgical exclusion of specific parts of the gastrointestinal tract from passage of the nutrients is one of the possible reasons for that effect [6].

Despite the vast research in this area, we still cannot explain the differences in gut hormones influence on the final result of various bariatric procedures.

Staple-line disruption (SLD) is a common complication of vertical banded gastroplasty, while gastrogastric fistula following gastric bypass is a rare entity [7].

Following uncomplicated RYGB, duodenal exclusion results in nutrients passing through the gastric pouch and directly entering the previously created Roux jejunal loop. SLD results in opening an alternative way through the remnant of the stomach, duodenum and first loops of jejunum. As a result, it can lead to preoperative eating habits and weight regain. Surgical revision with restoration of gastric pouch is indicated (Fig. 1).

In an attempt to better understand the physiological factors underlying response to bariatric surgery, we herein report our study of glucose homeostasis and hormonal changes following surgical repair of gastrogastric fistula.

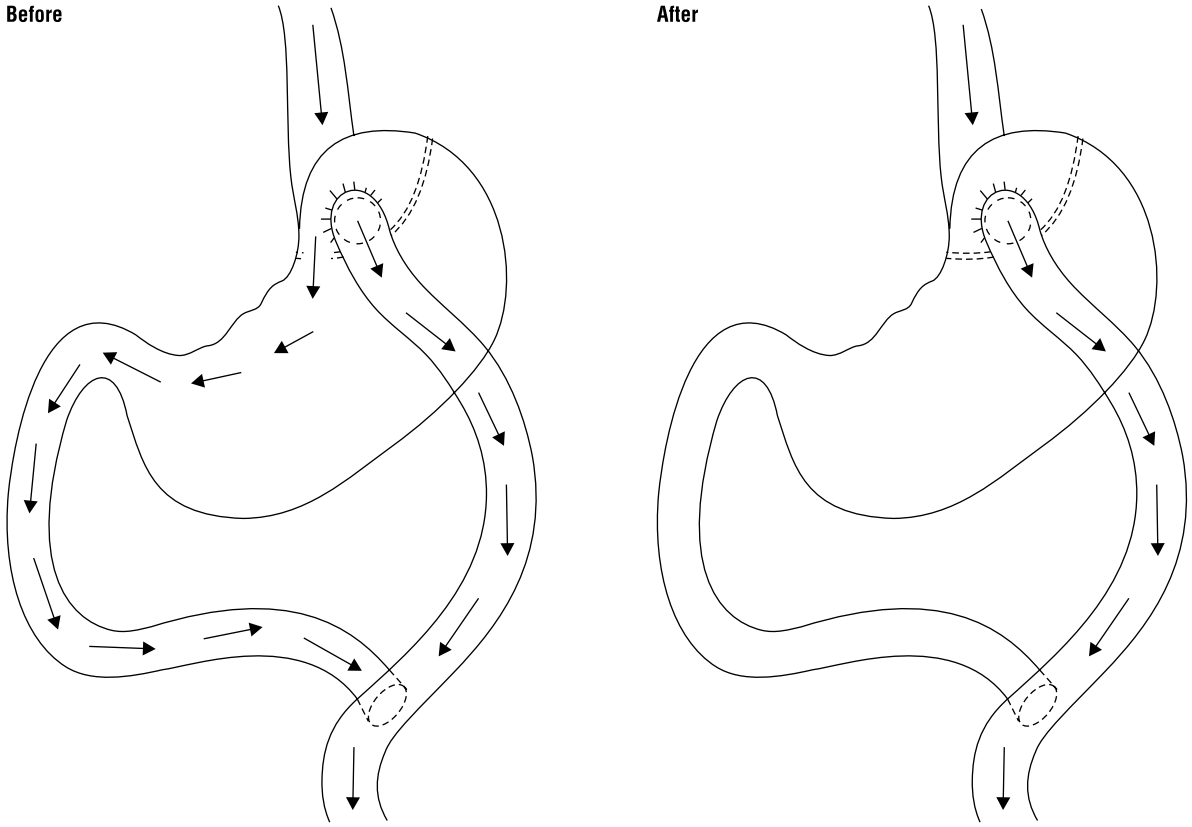

Figure 1. *Before — Preoperative two routes passage (Roux loop and alternative way through the remnant of the stomach, duodenum and first loop of jejunum). After — Postoperative Roux loop passage (after restoration of gastric pouch and duodenal exclusion)*

Rycina 1. *Przed — przedoperacyjne dwie drogi pasażu (pętla Roux oraz alternatywna droga przez żołądek, dwunastnicę i pierwszą petlę jelita cienkiego). Po —pooperacyjny pasaż przez pętlę Roux (po odtworzeniu proksymalnego zbiornika żołądkowego z wyłączeniem pasażu dwunastniczego)*

Material and methods

Among the patients investigated in the Department of General and Transplant Surgery of the Medical University in Lodz, Poland for weight regain following Roux-en-Y gastric bypass performed for morbid obesity, three subjects with endoscopically confirmed staple-line dehiscence were found. All of them were consented for surgery and operated on. On laparotomy, the restoration of gastric pouch was performed by transection of the stomach just below the staple line.

Patient characteristics are summarised in Table I. Each subject underwent an oral 75 g glucose tolerance test (OGTT) before (baseline) and one week after the surgery. Blood samples were centrifuged immediately at 3,000 rpm for ten minutes and stored at –80°C until assayed. Samples from our patients obtained before and after surgery were studied using the same commercial kits. Plasma glucose, pancreatic hormones (insulin and glucagon), small intestine incretin hormones (glucose-dependent insulinotropic polypeptide, GIP and glucagon-like peptide 1, GLP-1) were measured in the OGTT samples. Fasting plasma levels of appetite regulating hormones (ghrelin and leptin) were assessed before and after surgical re-intervention. All data is given in text and tables.

Results

The data from the three individual studied patients is shown in Tables II and III. Generally, duodenal passage exclusion in the studied group resulted in early improvement of control fasting plasma glucose with decrease of glucagon from 18.5 to 15 (by 19%), relatively stable insulin (Fig. 2) and decline of incretin hormones (GIP and GLP-1; Table IV). Post-challenge measurements confirmed amelioration of glycaemic control with decrease of plasma glucose from 182 to 158 mg/dL at 60 minutes (Fig. 2). Surgical re-intervention resulted in exacerbation of GIP response with a brisk rise in plasma level (Table IV), accompanied by a considerable increase of peak insulin concentration (Fig. 2). On the contrary, the overall post-challenge glucagon and GLP-1 responses were decreased. After gastric pouch restoration, a marked decrease in fasting plasma ghrelin and leptin were observed (Table II).

Table I. *Clinical characteristics of the patients included in the study*

Tabela I. *Charakterystyka kliniczna chorych zakwalifikowanych do badania*

N	Gender	Age	Date of surgery	Preoperative BMI [kg/m^2]	Nadir postoperative BMI [kg/m^2]	Date of diagnosis of SLD	Pre-reoperative BMI [kg/m^2]	Actual BMI [kg/m^2]
1	F	54	2003	56.79	32.45	2011 (eight years postoperatively)	44.62	34.13
2	M	51	2007	54.84	33.3	2010 (three years postoperatively)	49.86	27.7
3	M	46	2003	36.75	23.38	2011(eight years postoperatively)	34.41	27.73

Table II. *Glucose, glucagon, insulin, GIP and GLP-1 plasma concentrations of studied individuals in oral glucose tolerance test before (baseline) and one week after surgery*

Table II. *Stężenia glukozy, glukagonu, insuliny i GLP-1 w osoczu badanych osób oceniane w doustnym teście obciążenia glukozą przed (wartość wyjściowa) i tydzień po operacji*

Factor		Glucose [mg/dL]			Glucagon [ng/mL]			Insulin [IU/mL]			GIP [ng/mL]			GLP-1 [ng/mL]		
OGTT minute		0	60	120	0	60	120	0	60	120	0	60	120	0	60	120
Patient 1	Baseline	120	182	156	19.7	17.9	9.4	11.4	79.9	51.8	1.44	1.39	0.56	2.5	45.6	62.4
	One week	118	133	168	19	18.9	1.6	11.1	106.8	21.4	0.9	1.28	1.1	2.2	58.6	53.4
Patient 2	Baseline	113	216	165	23.3	8.3	9.2	5	61.5	50.1	2.1	0.75	1.1	1.3	92.3	98.5
	One week	104	211	157	15.7	6.3	8.9	4.8	78	43.7	1.9	3.8	1.5	0.8	26.6	36.7
Patient 3	Baseline	119	148	106	12.5	11.2	13.1	5.6	23.9	25.7	1.37	1.2	0.7	3.5	121	162.7
	One week	109	132	119	10.3	0.9	1	5.5	49.1	20.7	0.87	1.11	1.78	2.8	74.4	111

Table III. *Fasting ghrelin and leptin plasma concentrations of studied individuals before (baseline) and one week after surgery*

Tabela III. *Stężenia na czczo greliny i leptyny w osoczu krwi badanych osób, przed (wartość wyjściowa) i tydzień po operacji*

Factor	Timepoint	Ghrelin [ng/mL]	Leptin [ng/mL]
Patient 1	Baseline	58.6	30.98
	One week	47.4	28.83
Patient 2	Baseline	95.6	31.93
	One week	17.9	22.8
Patient 3	Baseline	25.15	30.53
	One week	18.2	24.13

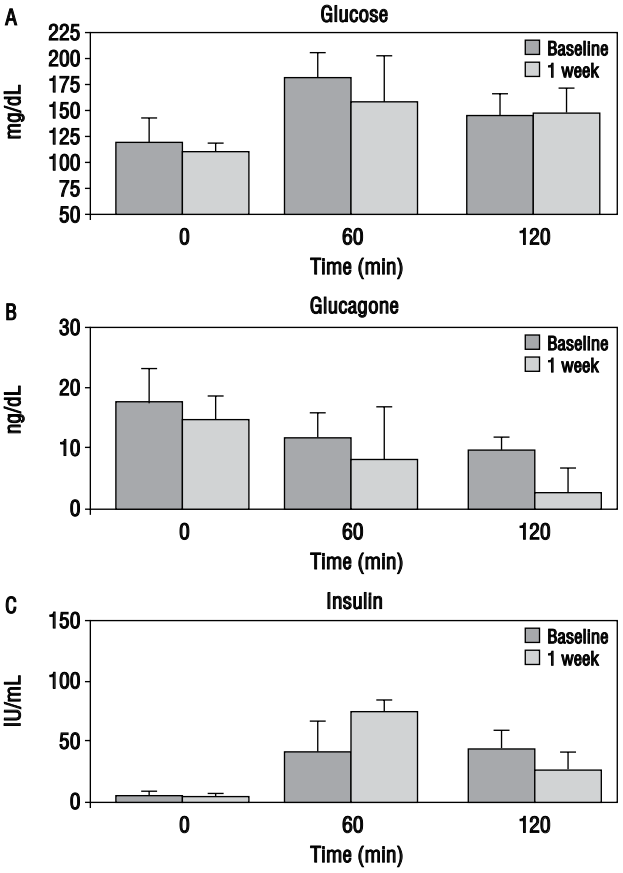

Figure 2. A. *Glucose (mg/dL);* **B.** *Glucagon (ng/mL) and* **C.** *Insulin (IU/mL) mean plasma concentrations (± standard deviations) in oral glucose tolerance test before (baseline) and one week after surgery*

Rycina 2. *Średnie stężenia* **A.** *glukozy (mg/dl);* **B.** *glukagonu (ng/ml) i* **C.** *insuliny w osoczu krwi (± odchylenie standardowe) oceniane w doustnym teście obciążenia glukozą (wartość wyjściowa) i tydzień po operacji*

Discussion

The main focus of this report is the comparison of glucose homeostasis before and after surgical re-intervention in IFG patients with SLD. Our study suggests that restoration of gastric pouch provides very early, moderate amelioration of glucose metabolism with improvement of fasting glucose level control and post-challenge glucose tolerance, yet without complete normalisation of glucose homeostasis at one week after surgery. Likewise, other authors [5] have indicated that marked improvement may occur very soon after bariatric surgery before significant weight loss. Nevertheless, there has been little assessment of the hormonal background of these changes shortly after surgically altered anatomy of different parts of the small intestine.

By studying patients with SLD before and one week after surgery, we found that duodenal exclusion resulted in a decrease of fasting level and exaggerated postprandial GIP response compared to the two routes passage (duodenal limb and Roux loop). The changes seen in this hormone after bariatric surgery are not consistent in the literature. Most reports have indicated that fasting [8], but also postprandial, GIP levels reduce after malabsorptive surgery [9], and only a few studies have reported an increase of glucose-stimulated GIP levels [10], likewise in our report. Some authors indicate that a decrease in GIP after a bariatric operation is beneficial [11]. This seems to be untrue, given the data on its glucose-dependent manner of stimulating insulin secretion. Postprandial insulin secretion improves rapidly after surgery [12], something also proven by our study. It occurs almost too immediately, and cannot to be explained by the weight loss. Our study suggests that surgically altered anatomy of foregut affects glucose homeostasis by GIP concentrations changes. Given that GIP triggers insulin secretion, it is possible that enhanced secretion of this incretin, rather than reducing insulin resistance, contributes to exaggerated postprandial insulin response in these subjects.

Numerous studies have reported that improvement in glucose tolerance after bariatric surgery is related to the increase of GLP-1 response [13]. In contrast, other reports have failed to show these discrepancies in fasting GLP-1 in the very short period after RYGB [14], although only fasting samples were measured.

In our study, we found that gastric pouch restoration in patients with SLD is associated with a decrease of GLP-1 secretion. This is entirely contradictory to most reports on hormonal changes after bariatric surgery [13], although, in these studies, a liquid test meal was used as the best manner of eliciting robust

Table IV. *Changes of GIP and GLP-1 plasma concentrations in oral glucose tolerance test and fasting plasma ghrelin and leptin before (baseline) and one week after surgery. Values are means plus or minus standard deviations*

Tabela IV. *Zmiany stężeń GIP i GLP-1 w osoczu krwi ocenianych w doustnym teście obciążenia glukozą oraz stężeń na czczo greliny i leptyny przed (wartość wyjściowa) i tydzień po operacji. Wyniki przedstawiono jako wartości średnie z odchyleniem standartowym*

Factor	Time	OGTT samples mean plasma levels ± SD		
		0 min	60 min	120 min
GIP [ng/mL]	Baseline	1.63 ± 0.4	1.11 ± 0.32	0.78 ± 0.28
	One week	1.22 ± 0.58	2.06 ± 1.50	1.46 ± 0.34
GLP-1 [ng/mL]	Baseline	2.43 ± 1.1	86.3 ± 38.05	80.9 ± 50.8
	One week	1.93 ± 1.02	53.2 ± 24.3	67.03 ± 38.98
		Fasting mean plasma levels ± SD		
Ghrelin [ng/mL]	Baseline	59.78 ± 35.23		
	One week	27.83 ± 16.94		
Leptin [ng/mL]	Baseline	31.15 ± 0.71		
	One week	25.29 ± 3.22		

responses of this incretin hormone [15]. Therefore, one might speculate whether our data is limited by nutrition-related bias, since consistent responses of GLP1 in T2DM were observed using meal tests but not glucose tolerance tests [16]. Furthermore, only control tests after primary RYGB in our patients would have clearly showed that the observed GLP-1 decrease is specific for gastric pouch restoration in patients with SLD. Thus, further studies are needed to elucidate these controversies. So far, it has been proved that in contrast to uncomplicated gastric bypass, purely gastric restrictive procedures are not associated with any changes in GLP-1 levels.

To date, as in our study, it has been found that elevated plasma glucagon markedly decreases in severely obese patients after gastric bypass [17]. This observation may be of physiological significance, since fasting hyperglucagonaemia and blunted response of glucagon are contributory to T2DM and may lead to fasting and postprandial hyperglycaemia. Future studies will be required to determine the specific role of the glucagon decrease and diabetes resolution after bariatric surgery.

Circulating ghrelin correlates inversely with body mass index (BMI) [18], but still the question as to whether the weight loss effect of RYGB depends on this hormone alterations requires to be clarified. Acute early decline in ghrelin levels, likewise in our subjects with diversion from two to one route passage, could be related to either intraoperative interference of the fundic vagal supply [19] or 'override suppression' of ghrelin-producing cells isolated from contact with enteral nutrients [20]. Several other groups have found that reduction in ghrelin is temporary, and that subsequently it tends to further increase above preoperative levels, indicating no relationship between changes of ghrelin signalling and weight loss after RYGB [21]. These discrepant results call for further elucidation.

Leptin concentration has been found to be decreased in obese patients after various bariatric surgeries [21], since it usually reflects the total amount of fatty tissue in the body. BMI is the main determinant of the decrease of serum leptin concentration long-term after surgery. The results of our subjects indicate that a significant decline of leptin occurs soon after surgical reintervention in SLD patients. This is consistent with previous knowledge that leptin might be regulated by a mechanism of foregut passage alterations with exclusion of duodenal limb. Early normalisation of leptin may induce further weight loss and glucose homeostasis improvement, with resolution of insulin resistance [8].

We acknowledge several limitations of our study. Firstly, as mentioned, we used a 75 g oral glucose tolerance test. The dynamic of gastrointestinal hormones response including incretins following this test is differentiated in various studies and might not be representative. Furthermore, major abdominal surgery may cause early, marked glucose homeostasis disturbances including stress hyperglycaemia that may obscure hormonal changes related to alteration of the small intestine anatomy. Nevertheless, our results went exactly in the opposite direction, with moderate amelioration of the glucose metabolism.

Conclusions

Our report gives further insight into the hormonal mechanisms underlying the effects of bariatric surgery on glucose homeostasis that is highly important, since it may facilitate novel conservative therapies of diabetes without the need for surgery.

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