EARLY RESULTS OF ROUX-EN-Y GASTRIC BY-PASS ON REGULATION OF DIABETES TYPE 2 IN PATIENTS WITH BMI ABOVE AND BELOW 35 KG/M²

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The idea of surgical treatment of type 2 diabetes was established in the U.S. and was based on observation of patients after bariatric operations. Performed in cases of morbid obesity exclusion of the duodenum and anastomose the stomach with the central part of the intestines cause shortened absorption of nutrients, what showed a beneficial effect on weight loss, resolution of comorbidities and reduce the risk of developing cardiovascular diseases and cancer. Analysis of the results of surgical treatment of obese patients with type 2 diabetes confirmed the usefulness of surgical methods.

The aim of the study was to evaluate the impact of Roux-en-Y gastric by-pass (RYGB) on diabetes in patients with BMI below and above 35 kg/m².

Material and methods. The study comprised 66 patients with DM2, who underwent Roux-en-Y gastric bypass due to morbid obesity (BMI above 35 kg/m²) and three patients with DM2 and BMI below 35 kg/m². In patients with DM2 and BMI < 35 kg/m² criteria for inclusion in the operational treatment were: DM2 difficult to be regulated pharmacologically lasting less than 10 years and BMI at the qualification about 35 kg/m². Indications have been determined on the basis of three consecutive measurements of HbA1c values above 7%, and measurements of blood glucose (frequent fluctuations in blood glucose levels on the value of hypoglycemia to hyperglycemia).

Results. The criteria for diagnosing resolution of DM2 included the level of HbA1c < 6% and glucose fasting level below 100 mg/ dl. In a group of 66 patients with DM2 and obesity, regression of DM2 was observed in 48 patients (73%) as early as during the hospitalization. In 11 patients (16.7%) glycaemia and HBA1c were stabilized within 8 weeks after surgery. In 7 (10.6%) cases of patients with difficult to control DM2, there was still need for antidiabetic medication, but glycemic control was much more effective. After one year remission was observed in 89% of patients. In all three patients with DM2 and BMI < 35 kg/m² total glycemic resolution of DM2 was observed during hospitalization. In this group there has been no postoperative complications. In the group of 66 obese patients with DM2 postoperative complications were found in 7 cases, they were related to infection and prolonged healing of surgical wound. One patient had an intraabdominal abscess located in the left subphrenic region, it was punctured under ultrasound guidance.

Conclusions. The ultimate evaluation of this method demands several years of meticulous clinical studies. Despite of that, considering high cost of life-long conservative therapy of DM2 and its complications, severe impact on quality of life and serious consequences of the disease, the surgical metabolic intervention may become the most resonable solution in many cases.

Key words: diabetes type 2, surgical treatment, Roux-en-Y gastric by-pass, incretines

Diabetes type 2 (DM2) has been known as contemporary pandemia or even plague of modern world. In 1995 there have been 135 million people suffering from diabetes type 2 worldwide, while estimates for 2025 predict that there will be more than 330 million of patients with DM2 (1). Polish data are similarly unfavourable, the number of patients with DM2 has doubled between 1986-2000 and currently the incidence in Poland reaches 7%,
comparatively to 2.6% incidence in other European countries and the USA.

DM2 is considered a social disease and has a significant impact on the funding spent on health care. The average cost of treatment of DM2 patient considerably exceeds mean cost of treatment of so called „random patient“. Those expenses include both direct (diagnostics, treatment and hospitalization) and indirect costs (sick leaves, early retirement, home care of patients). In the US the annual cumulated cost of treatment of DM2 patients reaches 100 billion dollars. In Poland, those costs are estimated at the level of 2.6 billion PLN, while the costs of treatment of complications of DM2 in 2002 was 431 million PLN (2).

DM2 is also one of the most frequent complication of another civilizational disease which is obesity – DM2 diagnosed in more than 20% of patients from that group.

Such situation has led to the increase in every potential alternative to the treatment of DM2 and its consequence.

Currently one of the most interesting alternatives is surgical treatment of DM2.

The idea of such approach has been based on the observation of the postoperative course of bariatric patients. Several studies have documented withdrawal of DM2 independent of pharmacotherapy in 47-70% of cases after restrictive procedures, 80-98% after RYGB and as much as 92-100% after biliopancreatic diversion (BPD) (3).

First attempts to utilize surgical intervention in DM2 therapy have been undertaken in 2004 by Rubino and Marescaux who treated Goto-Kakizaki rats (animal model of DM2) with BPD. In all of the examined animals DM2 disappeared within 3 weeks after surgery with average glicaemia of 96.3 ± 10.1 mg/dl (4).

In 2008-2009 there have been more than 1000 patients with DM2 treated surgically because of diabetes type 2, nevertheless American Diabetes Association (ADA) still claimed the method needs further clinical research. In March 2011 NY is going to be the host of the congress organized by European Association for Endoscopic Surgery (EAES) and ADA, aiming to set a new consensus on the role of surgical treatment of DM2 in non-obese patients. Less conservative attitude has been included in consensus of 53 experts in diabetes that has been reached in Rome in 2007. In that document the surgical treatment has been considered acceptable in patient with BMI 30-35 in whom the DM2 is difficult to control in a standard conservative way. Next step has been done in February 2010 during Diabetes Surgery University of Malaga meeting, when the participants concluded that metabolic surgery procedures could be performed in all patient in 18-65 years old with insulin-dependent, difficult to be controlled DM2, as well as in patients treated with oral antiglcaemic drugs who are considered to be transferred to insulin therapy (5, 6).

The aim of the study was to evaluate the impact of RYGB on diabetes in patients with BMI below and above 35 kg/m².

MATERIAL AND METHODS

Material

We present 66 patients with DM2, who underwent Roux-en-Y gastric bypass due to morbid obesity (BMI above 35 kg/m²) in 2008-2010. The study had a prospective nature. Another three patients with DM2 and BMI below 35 kg/m² were operated on in 2010 also with RYGB.

In the group of 66 obese patients with BMI >35 kg/m², (mean BMI = 42.3), there were 37 women and 29 men in age 37-62. In all patients RYGB was chosen due to concomitant diabetes type 2, as a potentially curative procedure. In 2010 three cases with BMI <35 kg/m² were also treated with RYGB. There were 3 females in age 26-60 and BMI at qualification of 30-31 kg/m² on the beginning of preoperative period and lower BMI at the time of the operation. The weight lose hasn’t improve the controlled glycemia (tab. 1). The average duration of DM2 in the group of obese patients was 8.2 years, in patients with BMI <35 kg/m² – 7 years.

Methods

In all cases, the preoperatively glycosylated hemoglobin (HbA1c) and the highest and lowest blood fasting glucose level were determined. In addition, the dose and type of antidiabetic agents (insulin vs oral agents) and the duration of the disease were taken into account. Similarly, the HbA1c was assessed every 4 weeks after surgery, glucose measured at 0
and 1 day after surgery, every 4 hours, then 4 times a day until discharge from hospital. Then, the levels of glucose have been observed for 8 weeks, presented as a daily average of three measurements. The reports of the need for diabetes medication after surgery were also evaluated. In patients with DM2 and BMI <35 kg/m² criteria for inclusion in the operational treatment were: DM2 difficult to be regulated pharmacologically lasting less than 10 years and BMI at the qualification about 35 kg/m². Indications have been determined on the basis of three consecutive measurements (at intervals of 3 months) with HbA1c values above 7%, and measurements of blood glucose (frequent fluctuations in blood glucose levels on the value of hypoglycemia <60 mg/dl to hyperglycemia <250 mg%).

The exclusion criteria in the group of patients with BMI <35 kg/m²:
1) diabetes lasted over 10 years,
2) positive anti-GAD antibody,
3) C-peptide levels <1 ng/mL – the diagnosis of DM1,
4) liver disease (e.g. cirrhosis, hepatitis C),
5) renal insufficiency (creatinine level <1.5 mg/dl),
6) hepatic ALT and AST levels <3x the value of reference,
7) cancer in patients history <5 years.

All the patients were qualified to RYGB. In a group of patients with morbid obesity in 5 cases the laparoscopic approach was used, in 61 cases a combined access: the initial step of operation – sleeve gastrectomy – was performed laparoscopically (typical location of ports), followed by a 10 cm left hypochondrion Kocher, which was made for manual entero-enteric anastomosis and stapled gastro-intestinal one. Such a modification access was dictated by economic reasons, as it allows for manual intestinal anastomoses. Roux-en-Y anastomosis was performed after exclusion of intestinal limbs biliopancreatic and digestive both with length of 120-130 cm. In patients with DM2 and BMI <35 kg/m² in 3 cases RYGB was performed (a typical gastric pouch with slightly larger capacity of about 100 ml), in all cases combined access was also used. The excluded limbs were: 80 cm from the Treitz ligament – the biliopancreatic limb and 60 cm alimentary one (fig. 1).

Routinely in all cases intraoperatively methylene blue or air-leak test was performed. On the 4th day postoperatively X-ray study of upper GI tract was done with contrast to evaluate the anastomotic leak. Postoperative follow-up took place according to the following schedule: the first visit – 4 weeks after surgery, followed by 3, 6, 12, 18 months and every year for the next 5 years.

**RESULTS**

The criteria for diagnosing resolution of DM2 included the level of HbA1c <6% and glucose fasting level below 100 mg/dl. The criteria for diagnosing resolution of DM2 included the level of HbA1c <6% and glucose fasting level below 100 mg/dl. In 7 (10.6%) cases of patients with difficult to control DM2, there was still need for antidiabetic medication, but glycemic control was much more effective. The average difference between the highest and the lowest measurements of blood glucose (Δ) 4 weeks after RYGB in this group was 68.3 mg/dl ± 10.4 mg/dl. The average

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**Fig. 1. RYGB in group with BMI <35 kg/m² and DM2**
HbA1c in the group of 66 obese patients, 4 weeks after surgery was 6.4% ± 0.8%, 8 weeks after RYGB 6.1 ± 0.43 (tab. 2).

In patients with DM2 and BMI <35 kg/m², similar curative criteria were used as for patients with morbid obesity. In all three cases treated in the second half of 2010 total glycemic resolution of DM2 was observed during hospitalization, without need for any hypoglycemic drugs within 12 weeks after surgery covered by follow-up (tab. 3).

In patients with BMI <35 kg/m² and DM2, there has been no postoperative complications and average hospital stay was 4.3 days. In the group of 66 obese patients with DM2 postoperative complications were found in 7 cases, they were related to infection and prolonged healing of surgical wound. One patient had an intraabdominal abscess located in the left subphrenic region, it was punctured under ultrasound guidance and drained percutaneously for 10 days. The average period of hospitalization in this group was 6.2 days.

**DISCUSSION**

The main reason behind the incidence and progression of DM2 are increasing insulin resistance together with impaired endocrine function of pancreatic beta cells (7). This dysfunction results in lack of ability to produce insulin in response to changes of glicaemia. Despite hypoglycemic oral therapy or even institution of insulin, further progressing beta insufficiency is being observed. It is suspected that the background of this pathology is associated with defect of intestinal hormones – incretines, that constitutes mostly of decreased secretion of glucagon-like peptide (GLP-1) with maintained its insulinotropic effect. At the same time the secretion of gastric inhibitory peptide (GIP) is within physiologic values but its effectiveness is severely impaired. Incretines act in various directions. First, they increase the production of insulin by beta cells and suppress secretion of glucagon. Second, they slow down the stomach emptying and suppress apetite. They also are supposed to increase peripheral insulin susceptibility. In patients with DM2, GLP-1 secretion has been proved to be decreased (8, 9). It has been noted that after RYGB the secretion of GIP drops in patients with DM2, while this has not been presented in non-diabetic obese patients (10).

It is the incretin effect that has been perceived as the most important mechanism behind the miraculous disappearance of diabetes after RYGB unrelated to the loss of weight. It has been also been hypothesied that an unknown biochemical signal/hormone can be produced in duodenum. This signal/hormone would be responsible for resistance of the peripheral tissues to insulin. It has also been speculated that one or more unknown substances, possibly blocking insulin activity, can be produced in the initial part of small intestine, those substances are called anti-incretines (11, 12).

Duodenal by-pass and surgical connection of the stomach with medial part of jejunum results in shortening of the period of absorption of nutrients, which directly leads to the weight loss. The results of surgical treatment of obesity has been proved to be successful in reducing body weight, but also in resolution of

Table 2. Results of RYGB in group of patients with DM2 and BMI >35 kg/m²

<table>
<thead>
<tr>
<th>HbA1c before RYGB%</th>
<th>Δ mg/dl (highest/lowest glycemia level)</th>
<th>HbA1c (%) 4 weeks after RYGB</th>
<th>HbA1c (%) 8 weeks after RYGB</th>
<th>HbA1c (%) 12 weeks after RYGB</th>
<th>Δ mg/dl 4 weeks after RYGB</th>
<th>DM2 resolution % of cases after RYGB in 4 weeks</th>
<th>DM2 resolution % of cases after RYGB in 8 weeks</th>
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<td>7, 6 ± 0,7</td>
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<td>6,4 ± 0,8</td>
<td>6,1 ± 0,43</td>
<td>5,5 ± 0,31</td>
<td>68,3 ± 10,4</td>
<td>73</td>
<td>16,7</td>
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Table 3. Results of RYGB in group of patients with DM2 and BMI <35 kg/m²

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<th>No</th>
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<th>Δ mg/dl (highest/lowest glycemia level)</th>
<th>HbA1c (%) 4 weeks after RYGB</th>
<th>HbA1c (%) 8 weeks after RYGB</th>
<th>HbA1c (%) 12 weeks after RYGB</th>
<th>Δ mg/dl 4 weeks after RYGB</th>
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concomitant diseases as well as alleviating risks of vascular diseases and cancer. The analysis of the results of surgical treatment of obese patients with DM2 has also proved unquestionable effectiveness. The normalization of gliceaemia has been observed in most of the patients within few weeks postoperatively and in some of them as early as during the hospitalization (13).

Rubino et al. published studies in 2006 and 2010 in which they emphasise the role of gastrointestinal tract endocrine mechanisms and underline the issue of duodenal exclusion from the nutrient passage as more important than faster transportation of nutrients to the terminal part of ileum, where incretines are produced (14, 15).

Encouraging results have been presented by Schauer et al. on the basis of 240 bariatric patients with obesity, in whom in 80% not only insulin but oral hypogliceaemic drugs could been discontinued postoperatively (16).

In the study by DePaula presenting the results of surgical treatment of non-obese patients with DM2 with BMI 20-34 kg/m², the complete resolution of DM2 has been achived in 64.7% of patients (HbA1c <6%). In 26.5% of patients periodical gliceaemia control and oral hypoglicemic drugs were needed (HbA1c 6-7%), while in 8.8% only improvement in control of diabetes has been reached (HbA1c <8%) (17).

An interesting comparison has been undertaken by Geloneze et al. 180 patients with diabetes type 2 have been dichotomized to surgical treatment vs. conventional treatment – control group (CG). At 24 weeks after surgery, patients experienced greater reductions on fasting glucose (14% vs. 7% on CG), HbA1c (from 8.78 to 7.84 in RYGB – p<0.01) and 8.93 to 8.71 in CG; p<0.05 between groups) and reductions on average daily insulin requirement (93% vs 29%, p<0.01). Ten patients stopped insulin usage in RYGB group but they remained on oral hypoglycaemic medications (18).

In metaanalysis presented by Fried, the criteria of diabetes type 2 resolution were relatively strict (fasting glicemia <99 mg/dl, HbA1c <6% plus complete lack of any DM2 conservative treatment). Positive result has been presented in 81.8% of cases with RYGB and BPD considered most effective (19).

Summarizing, the results published worldwide seem so promising that they encourage the use the bariatric procedures with exclusion of initial part of small intestine in patients with diabetes and obesity as well as with normal body weight (20, 21).

The experience of the authors of this study arising from 66 RYGBs in patients with BMI above 35 kg/m² and three RYGBs in patients below 35 kg/m² supports optimistic point of view on the future of metabolic surgery in Poland. Both reduction of the biochemical measures of DM2 (glicemia, HbA1c) as well as lack of necessity for any hypogliceaemic drugs one month after surgery support international enthusiasm about this alternative in treatment of DM2. It should be remembered that the level HbA1c as early as 4 weeks after RYGB does not always have to be within normal values, as HbA1c reflects the highest level of glicemia in previous 120 days. Therefore, this measurement should not be considered as the most relevant proof of DM2 resolution in the early post-operative period.

The modification of the surgical access – combined laparoscopic and open – has been chosen due to economic reasons, as manual jejunal-jejunal anastomosis is associated with low cost at similar risk of complications and only insignificant prolongation of the procedure.

CONCLUSIONS

The ultimate evaluation of this method demands several years of meticulous clinical studies. Despite of that, considering high cost of life-long conservative therapy of DM2 and its complications, severe impact on quality of life and serious consequences of the disease, the surgical metabolic intervention may become the most resonable solution in many cases.

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Received: 11.12.2010 r.
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