

Alternative ways to correct poor glucose metabolism in patient with diabetes mellitus

Leonid Sevastyanov¹, Yermek Turgunov¹, Jean-Pierre Faure², Dmitriy Shestakov¹

¹Karaganda Medical University, Kazakhstan

²University of Poitiers, France

Received: 2021-08-09.

Accepted: 2021-09-27



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J Clin Med Kaz 2021; 18(5):30-34

Corresponding author:

Leonid Sevastyanov.

Email: Sevastyanov@kgmu.kz;

ORCID: 0000-0002-8071-8690.

Abstract

There is an annual increase in the incidence of diabetes recorded worldwide. The existing measures of prevention and multimodal treatment of the disease have not yet brought the desired results. A promising field is bariatric (metabolic) operations used in obese patients, which also improve glucose metabolism in the case of concomitant diabetes mellitus of both types 1 and 2. At the same time, there is a certain contradiction and understatement regarding the mechanisms that lead to remission of diabetes mellitus, regardless of weight loss. One of the anatomical effects of bariatric procedures is the accelerated release of nutrients into the distal segment of the small intestine, which leads to stimulation of enteroendocrine cells and increased secretion of incretins (GLP-1, PYY, etc.). The experiment investigates these mechanisms by the operation of ileal transposition. Further study of the ileal transposition effects using different models of type 1 and type 2 diabetes, accompanied both with and without obesity, may contribute to a more detailed understanding of the triggering and supporting mechanisms of increasing glucose tolerance in the struggle against this disease.

Key words: diabetes mellitus, metabolic surgery, ileal transposition

Introduction

Diabetes mellitus is a chronic, progressive, widespread disease, with a steady upward trend worldwide. Various aspects of diabetes are well described: morbidity, early and late complications of the disease, impact on the quality of life and health care costs, mortality, etc.

The International Diabetes Federation (IDF) assessed the overall prevalence of diabetes mellitus: if in 2011, it was diagnosed in 366 million patients, then by 2030, it is projected to be found in 552 million patients. According to WHO, in 2014, the number of patients was 442 million adults, compared to 1980, when the number of people suffering from this disease was 108 million [1,2].

Every year, huge funds are allocated for the treatment of diabetes. In total, \$760 billion was spent worldwide in 2019 to combat this disease [3].

It is shown that patients with diabetes mellitus have a high risk of disability and cardiovascular diseases, compared with people who do not suffer from this pathology. Moreover, this risk tends to increase over time since the lack of good metabolic control, which is

evidenced by constantly increased levels of glycosylated hemoglobin (HbA1c), inevitably leads to complications: diabetic nephropathy, diabetic retinopathy, diabetic neuropathy, as well as macrovascular problems [4].

The coronavirus pandemic has forced a new insight into diabetes mellitus as a life-threatening situation when combined with COVID-19. There are indications that diabetes is not a risk factor for COVID-19 but it has an aggravating effect on its course and outcome [5].

Treatment of patients with diabetes, of course, leads to an improvement in their condition and gives a certain economic effect [6]. However, physiological and, therefore, the most affordable measures, i.e. changing the lifestyle and diet, do not achieve significant long-term results [7] and drug therapy only causes compensation in 30% of patients, while remission is achieved only in a minimal number of patients [8].

Therefore, the relevance of the problems of diabetes mellitus today remains high. Efforts to solve these problems should probably be aimed at searching for new methods of treating and preventing the development of diabetes using advanced technologies.

Effect of Bariatric Operations on Glucose Metabolism.

Recent studies have revealed and, subsequently, confirmed the positive effect of bariatric operations in patients with type 2 diabetes mellitus (DM2), both with and without obesity. Bariatric operations (baros = weight) is a surgical procedure performed on the gastrointestinal tract in patients with pathological obesity. Such operations are often referred to as metabolic operations because of their positive effects: weight loss and improved

metabolic control, especially in patients with DM2. Obviously, these effects have allowed several authors to consider a bariatric surgery as an alternative to pharmacological treatment, which can help to correct overweight, control hyperglycaemia, and achieve remission of the disease [9-20]. A number of studies have shown that surgical methods were successful and improved the condition of patients with diabetes mellitus of type 1 (DM1) [21-23] (Table 1).

Table 1 Bariatric surgery and diabetes: literature review results

Procedure	Procedure	Following time (years)	HbA1c	(%)	Remarks
Adams et al.[15]	418 RYGB (93 T2DM) 417 nonsurgical obese control (106 T2DM 321 population-based control (92 T2DM)	6	< 6.5	62% complete remission	Better control of bypass than nonsurgical group Mean BMI 45.9
Arterburn et al.[16]	4434 RYGB	5	< 6	68% complete 9% partial	Retrospective cohort
Cohen et al.[17]	66 RYGB	6	< 6.5	88% complete 11% partial	30 < BMI < 35
Lakdawala et al.[18]	52 RYGB	5	< 7	58% complete 38% partial	30 < BMI < 35 96% improvement Of metabolic status
Heneghan et al.[19]	52 RYGB, LSG, LAGB	5	< 6.5	44% complete 33% partial	Mean BMI 49 ± 8.7
Sultan et al.[20]	95 LAGB	5	< 6	40% complete 40% partial	Mean BMI 46.3
Scopinaro et al.[16]	312 BPD	10	ND	97%	
Pontiroli et al.[16]	23 BPD 78 LAGB 37 control	5.5	ND	100% 66% none	
Marceau et al.[16]	1356 DS (377 T2DM	7	ND	92%	

BPD - biliopancreatic diversion, LAGB - laparoscopic gastric band, RYGB - Roux-en-Y gastric bypass, LSG laparoscopic sleeve gastrectomy, DS duodenal switch, ND not defined.

A meta-analysis conducted by Zh. Khorgami et al. (2019) showed that within 2 years, 138 patients out of 263 who underwent surgery experienced remission of type 2 diabetes, compared to 7 out of 200 who received medication only. There was also a more significant decrease in HbA1C, serum glucose, increased HDL, and decreased triglycerides [24].

Bariatric operations that are the subject of the analysis are divided into restrictive (sleeve gastrectomy (SG) and regulated gastric banding (GB), malabsorption (intestinal bypass anastomosis), and combined, as well as combined/restrictive and malabsorbing (Roux-en-Y gastric bypass (RYGB) and biliopancreatic bypass with or without a duodenal switch, BPD or BPD-DS).

Studies have found [13,14] that remission of DM2 occurs in 66%, 45%, 80-85%, and 95% of patients after SG, GB, RYGB, and BPD-DS, respectively. The mechanism of remission of DM2 after bariatric surgery is still debated.

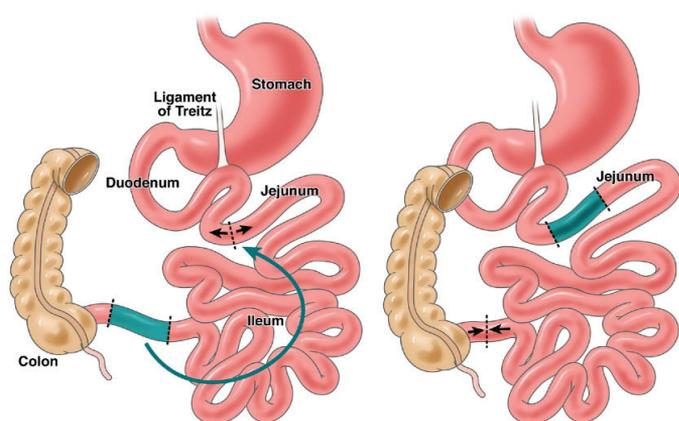
Thus, the most effective procedures for the induction of remission in type 2 DM are RYGB and BPD-DS [19-23]. Both procedures involve the exclusion of the duodenum from the digestive process and this mechanism was assumed to be required the effect of the operation, which has been confirmed by experimental studies by Rubino and Marescaux [30]. However, another anatomical effect of these operations is the

accelerated discharge of partially digested nutrients and their contact with the distal segment of the small intestine, the ileum, which contributes to the secretion of peptides of intestinal origin involved in glucose homeostasis [9].

To study the role of the distal segment of the ileum in RYGB surgery, the ileal transposition operation is used in the experiment [31], and the authors have shown that the procedure itself induces remission of type 2 diabetes and weight loss without a component of disabling the duodenum [32], but this opinion is controversial.

The ileal transposition (Figure 1), as an experimental operation, has found its origin in the work of H. Koopmans et al. (1982), who, while studying the effects of a jejunoileal bypass, particularly, a decrease in food intake, suggested the presence of an endogenous signal from the distal segments of the ileum in response to stimulation by food masses. In order to confirm this assumption in the experiment, the authors performed a resection of 10-20 cm of the distal part of the ileum in rats, followed by its movement on the neurovascular bundle to the proximal segments of the jejunum. The procedure was called the ileal transposition, and for the first time, there was a decrease in the amount of food consumed, body weight, glucose, triglycerides, and cholesterol levels with a preserved length of the small intestine [8].

Figure 1 - Scheme of Ileal transposition



Some clinical studies combined the ileal transposition with gastric bypass surgery or sleeve gastrectomy [33-36]. During a study of the metabolic effects of the ileal transposition in combination with elevating sleeve gastrectomy (DSG) in 159 patients with obesity and DM2, Celik et al. found a decrease in the average body mass index (BMI) from 39.33 to 25.51, the average fasting glucose level from 189.9 to 123.5 mg/dL, and the average HbA1c level from 9.24% to 6.14% a year after surgery [31].

The "Hindgut" hypothesis tries to explain the metabolic effects of the ileal transposition and states that the improvement in metabolic control is due to an increase in the flow of unabsorbed nutrients in the distal segment of the small intestine. Which leads to the activation of a neuroendocrine negative feedback mechanism often referred to as the "ileal inhibitor." This thesis is proved by the established effects of displacement of the distal segment of the small intestine in the experiment, i.e. the increase in the number and secretory activity of L-cells of the displaced segment of the intestine, increase in the secretion of glucagon-like peptide 1 and -2 (GLP-1, GLP-2), peptide tyrosine-tyrosine (PYY), increase in the mass of β -cells of the pancreas, decrease in their apoptosis and increase in insulin production, and increase in glucose tolerance [38,39,40].

GLP-1 increases glucose-induced insulin secretion, inhibits glucagon secretion, reduces food absorption, improves insulin sensitivity, promotes β -cell regeneration, and reduces their apoptosis, this is how its antidiabetic effect is manifested [41]. PYY, as well as GLP-1, is characterized by stimulation of β -cell regeneration and hypoglycemic effect. Moreover, it participates in the regulation of appetite by reducing it [42].

Another effect of the ileal transposition is to reduce gluconeogenesis and lipogenesis in the liver. In a study by Hung C. et al., the following was observed in rats after the ileal transposition: undigested food passing into the gut lumen triggered the production of chemokines, which reached the liver via the portal vein, therefore, it led to a decrease in the synthesis of glucose and lipogenesis in the body by attenuation of signaling via TGF- β and, consequently, a decrease in the level of hyperglycemia.

The ileal transposition proved to be the most successful metabolic operation in the correction of severe forms of nonobese DM2 in the experiment [43].

In addition, some authors express doubts about the pathophysiological importance of the hypothesis «Hindgut», which is due to the absence of an effect equivalent to metabolic operations in response to antidiabetic drugs stimulating secretion GLP-1 [44]. In contrast to the positive effects of the incretin

mechanism and the hypothesis «Hindgut», it is assumed that there are hormonal pathways with adverse effects for glycemic homeostasis, the so-called anti-incretin mechanism, which is launched in response to the passage of nutrients through the proximal sections of the small intestine and the presence of which explains the opposite «Foregut» theory. The anti-incretin effect is expressed in the inhibition of the incretin effect: it causes a decrease in insulin release, a decrease in beta cell proliferation, and inhibition of insulin action to prevent hypoglycemia. [45,46,47].

In this case, it is interesting to study the effects of IT and to develop innovative experimental operational methods, which make it possible to assess changes in the parameters of glycometabolism on DM models with the exception of the anti-incretin mechanism.

The Effectiveness of Bariatric Surgery in DM1.

To date, there is evidence that metabolic operations may improve the condition of patients with DM1 but the data of various authors are contradictory and further research is needed [15,17] in this field.

Initially, it was suggested that the improvement in the condition of patients with DM1 and their increased sensitivity to insulin is due to weight loss after bariatric surgery [48,49]. Currently, the Hussain study (2019) is known, which investigated changes in HBA1c, BMI, and the daily dose of insulin replacement therapy after bariatric interventions in patients with DM1. A decrease in these indicators was revealed but they were statistically unreliable for glycolized hemoglobin. A weak correlation between insulin dose and BMI, as well as a slight correlation between HBA1c and BMI after surgery, was found. According to the author, this dictates the need for further investigation of glucose homeostasis depending on the anatomical changes in the gastrointestinal tract caused by metabolic surgery since each centimeter of the gastrointestinal tract is a complex functional unit, thus, any change affects homeostasis [21].

Nevertheless, A. Chow et al., having conducted a meta-analysis, obtained statistically reliable results. The authors analyzed 13 papers describing the results of Roux-en-Y gastric bypass surgery in 86 patients with obesity and type 1 diabetes mellitus. It was found that their BMI ($p < 0.00001$), the need for insulin ($p < 0.00001$), and the level of glycolized hemoglobin ($p < 0.01$) decreased. However, the target value of HBA1c $\leq 7.0\%$ was not reached. According to the authors, this was due to an increase in the tolerance of the liver and peripheral tissues to insulin, instead of the effect of GLP-1 on the functions of the endocrine part of the pancreas since patients with DM1 had almost zero functional potential of beta cells [23].

According to Ahn C. H. et al. (2020), the ileal transposition slows the physiological aging of pancreatic β -cells in obese rats, which may contribute to an increase in insulin release following a meal. The mechanism underlying the prevention of the β -cell aging after the ileal transposition may be a new therapeutic target for diabetes mellitus.

It can be concluded that the metabolic effects of the ileal transposition cannot positively affect glycemic control in cases with minimal or zero β -cell functioning in patients with DM1. However, there is an assumption that islet cell regeneration occurs even in patients with long-term DM1. Therefore, the timing of bariatric surgery is crucial since effects mediated by the ileal transposition may contribute to the preservation of β -cell mass [50-52].

Conclusion

Interest in metabolic surgery for diabetes mellitus is growing from year to year. Particularly, when searching for the key expression of "ileal transposition," more than 300 publications are found in the Pubmed (US National Library of Medicine National Institutes of Health) database. The growth trend of publications has an upward exponential dependence.

Modern bariatric procedures, such as RYGB, BPD/DS and transit bipartition, which involve the mechanism of accelerated intake of undigested nutrients to the terminal segments of the

small intestine, are the most effective in the correction of morbid obesity and DM. Changes in the anatomy of the gastrointestinal tract during bariatric surgery mediate changes in hormonal regulation that contribute to the remission of diabetes, which requires further study by experimental operations.

Given the absence of an implemented surgical method for the treatment of diabetes mellitus without morbid obesity in clinical practice, the inconsistency and lack of data on the positive metabolic effects of the ileal transposition, it seems appropriate to further study the mechanisms of homeostasis of glucose during experimental operations.

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