Metabolic Endoscopy: Development and Perspectives

Dirk Raddatz

Department of Gastroenterology and Endocrinology, University Medical Center Goettingen, Goettingen, Germany

Keywords

Obesity · Type 2 diabetes mellitus · Endoscopy · Aspiration therapy · Duodenal-jejunal bypass sleeve · Duodenal mucosal resurfacing · Endoscopic sleeve gastropasty · Intragastric balloon · Primary obesity surgery endoluminal

Abstract

Background: Obesity and its metabolic sequelae are among the most serious challenges faced by health systems today and they are expected to pose a serious threat in the future as well. Therapy ranges from lifestyle modification to drug treatment to surgery. Metabolic endoscopy (ME) might close the gap between invasive “metabolic” surgery and conservative, less effective treatment. In recent years, several endoscopic approaches have emerged, promising a safe and effective approach to cope with obesity. Data on metabolic endpoints is scarce. This article will therefore highlight procedures with data on type 2 diabetes mellitus (T2DM) as the most prominent component of the metabolic syndrome. **Summary:** Most procedures showed beneficial effects in terms of weight reduction. For gastric procedures, there were no systematic studies primarily addressing parameters of glucose metabolism or diabetes outcomes. Metabolic benefit, if there is any, is most likely a by-product of weight loss. By contrast, duodenal-jejunal bypass sleeve (DJBS) is conceptually an antidiabetic procedure. Although adverse events are frequent, recent data points to a positive benefit-risk ratio. **Key Messages:** ME has the potential to constitute

a growing field in the treatment of obesity and associated T2DM. While data published on glycaemic parameters in restrictive approaches is not sufficient, there is strong evidence that malabsorptive DJBS has an antidiabetic “plus” effect. Further studies are necessary to define the role of ME within a lifelong concept of treating obesity and T2DM.

© 2019 S. Karger AG, Basel

Introduction

The number of obese individuals is continuously on the rise, making obesity a serious public health concern in the present and in the future. This is particularly of interest, since many diseases are linked to obesity; epidemic diseases such as type 2 diabetes mellitus (T2DM), cardiovascular diseases and several kinds of cancers are some examples of such diseases. Diet, sports and behavioural modifications are the mainstay of conservative treatment. However, these measures alone are seldom sufficient. Treatment of metabolic comorbidities such as T2DM and hypertension places a high financial burden on health care systems. Bariatric surgery offers an effective solution for many patients, but resources are not sufficient for conducting population-wide surgical programmes. Furthermore, surgery is not reversible, has immanent procedural risks, not all patients are willing and for some of them it might be an overtreatment.

Table 1. Summary of the studies discussed in the text

Procedure	Author	Year	<i>n</i>	EBWL, %	EBWL, % (<i>n</i>)	TBWL, %	TBWL, <i>n</i>	ΔHbA1c, %	HbA1c, <i>n</i>	FBG delta, mg/dL	FBG delta, <i>n</i>
a Controlled studies											
AT	Thompson et al. [12]	2017	207	21.7		8.6		-0.14			
DJBS	Jirapinyo et al. [17]	2018						-0.9	116 (4)		
DJBS	Kaplan et al. [23]	2016	320			5.5		-0.8			
DJBS	Laubner et al. [18]	2018	333	34.4		11.5		-0.86			
DJBS	Rohde et al. [16]	2016	235	12.6				-0.8*	49 (2)	-49*	49 (2)
DJBS	van Rijn et al. [20]	2017	48	7.6		1.2		0.1*			
IGB	Popov et al. [3]	2017		22.3	481 (3)	5.9	647 (8)	-1.1	63 (3)	-12.7	555 (5)
POSE	Miller et al. [10]	2017	39	26.9		8.1					
POSE	Sullivan et al. [11]	2017	332	11.8		3.6				-3.4	
b Observational studies											
AT	Nystrom et al. [13]	2018	201	46.3		18.2		-1	13	-7.9	
DJBS	Jirapinyo et al. [17]	2018		36.9	301 (4)	18.9	352 (10)	-1.3	388 (14)	-44.6	164 (9)
DJBS	Laubner et al. [18]	2018	235	28.5		11.7		-1.3			
DJBS	Patel et al. [19]	2018	45			13		-0.8			
DJBS	van Rijn et al. [20]	2017	185	46.3		12		-0.5			
DJBS	Forner et al. [21]	2017	114			10.5		-0.1			
DMR	Rajagopalan et al. [25]	2016	39			3		-1.2			
ESG	Sharaiha et al. [7]	2017	91			17.6		-1	18		
IGB	Popov et al. [3]	2017								-8	768 (18)

* Not significant. For meta-analyses, the number of studies is given in parentheses.

AT, aspiration therapy; DJBS, duodenal-jejunal bypass sleeve; DMR, duodenal mucosal resurfacing; ESG, endoscopic sleeve gastroplasty; IGB, intragastric balloon; POSE, primary obesity surgery endoluminal.

As a matter of consequence, various endoscopic procedures emerged to close the gap between conservative therapy and bariatric surgery. In 2011, a joint task force American Society for Gastrointestinal Endoscopy and the American Society for Metabolic and Bariatric Surgery defined criteria that endoscopic bariatric therapy should meet to be considered for clinical application in a “preservation and incorporation of valuable endoscopic innovations” (PIVI) paper [1]. While quantitative goals such as reduction of total body weight and excess weight loss (Editor 1) are well defined there, metabolic goals are less concrete.

Recently, the term “metabolic endoscopy (ME)” was coined as an analogy to “metabolic surgery”. While there are many actual reviews on endoscopic bariatric therapies [2], this article will provide an overview with particular focus on obesity and concomitant T2DM, making it “ME”.

Procedures can be categorized roughly according to the mechanism of action: (1) gastric restriction or (2) malabsorption. In the following sections, techniques and results will be presented accordingly. An overview of current studies is given in Table 1.

Restrictive Technologies

Restrictive procedures may induce early satiety by decreasing gastric capacity and/or modifying hormonal signals. This might be achieved either by filling gastric space or by altering gastric anatomy.

Intragastric balloon

While an older model was removed from the market in the early 1990s, the B.IB, currently named Orbera™ intragastric balloon (IGB) System (Apollo Endosurgery Inc, Austin, TX, USA), was approved for use in Europe in 1997 and in the United States in 2015. Since then, 2 other balloon systems have been approved by the FDA: the ReShape® Integrated Dual Balloon System (ReShape Medical, Inc., San Clemente, CA, USA) and the swallowable Obalon (Obalon Therapeutics, Inc.).

Despite a large number of trials on weight loss, information regarding metabolic benefits through IGB is limited. In a meta-analysis, Popov et al. [3] extracted 40 suitable studies (10 controlled, 30 observational, 5,668 [QCE2] patients) including at least 1 metabolic parameter. The author’s assessment on overall data quality was

rated “moderate” at best on almost all outcome issues. With respect to HbA1c, quality was even “low” with only 3 studies including 63 patients. Therein, the authors found a mean reduction of HbA1c of 1.1%. Data on fasting blood glucose was more robust. A mean difference of 12.7 mg/dL was found in 5 randomized controlled trials with a total of 555 patients. In 12 observational studies, HbA1c decreased 0.6% on average, suggesting a certain antidiabetic effect of IGB.

Only 1 observational study provided follow-up data on diabetes: the prevalence was 20.9% at balloon removal, compared to 32.6% at baseline [4].

The Spatz3 balloon (Spatz FGIA, Inc., Great Neck, NY, USA) might be more advantageous, since it can remain in place for 12 months instead of 6, and it is adjustable, resulting in superior responder rates [5]. Whether this advantage will translate to metabolic improvements is not certain. Studies including patients with diabetes have not been conducted to date.

Global incidence of death associated with ORBERA was reported to be less than 0.01%. Nevertheless, the FDA has issued warnings to health care providers regarding the risk of balloon hyperinflation, pancreatitis and death, and another 12 IGB-related deaths have been reported since then [6].

Gastric Suturing and Plication

Endostich

Endoscopic sleeve gastropasty (ESG) is a technique where the gastric volume is reduced by a number of full wall sutures with the help of an over-the-scope suturing device (“Apollo Overstitch” Apollo Endosurgery, Austin, TX, USA). In a prospective single-arm study with 91 participants, weight loss was moderately effective with a total body weight loss (TBWL) of approximately 17.6% [7]. ESG reduced hypertension, markers of diabetes, transaminases and hypertriglyceridemia. In 19 patients with diabetes, the HbA1c fell from 6.6 to 5.5%, 5 patients discontinued insulin and 2 discontinued all diabetes medications. First results suggested that similar effects can also be achieved with an alternative suturing system (Endomina single-use triangulation platform, Endo Tools SA [ETT], Gosselies, Belgium) [8]. The American Diabetes Association recommends an HbA1c of less than 7% as a reasonable goal for many patients [9]. Of note is that most patients in the Overstitch study were already within their target goals even before intervention, so that the question whether TDM2 patients with worse glycaemic control benefit from ESG remains unanswered.

Primary Obesity Surgery Endoluminal

The principle of primary obesity surgery endoluminal is to create folds in the stomach wall, thereby reducing the overall capacity and delaying gastric emptying. This is achieved by applying tissue anchors to the gastric fundus and antrum utilizing a peroral incisionless operating platform (USGI Medical, San Clemente, CA, USA). In a controlled trial, TBWL was 7.7% greater than in controls [10]. In another randomized controlled trial, the benefit on bodyweight was only 3.56% and the only metabolic parameter with significant improvement was fasting glucose [11].

Aspiration Therapy

Aspiration Therapy (AT) is accomplished by inserting a large gastrostomy tube (A-tube, Aspire Bariatrics, King of Prussia, PA, USA) by gastroscopy, very similar to a standard percutaneous endoscopic gastrostomy procedure. Irrigation and drainage are performed by patients, thereby removing approximately 30% of the ingested calories. The “PATHWAY” trial with 207 participants showed 8.6% greater reduction of TBWL in AT compared to lifestyle counselling alone [12]. The procedure is safe. The spectrum of adverse effects is very similar to that of the percutaneous endoscopic gastrostomy procedure, which has been known for decades. Compared to other endoscopic approaches, AT is possible for a relatively long term. A recent European registry study reported that AT therapy was performed up to about 4 years. The rate of participants decreased from 199 to 12 over time. After 52 weeks, all cardio-metabolic parameters improved. In a subgroup of 13 diabetic patients, HbA1c was reduced significantly by 1% from 7.8% at baseline to 6.8% at 1 year [13].

Malabsorptive Techniques

Endobarrier

Endobarrier (EB, GI Dynamics, Inc., Watertown, MA, USA) or duodenal-jejunal bypass sleeve (DJBS) consists of a sleeve proximally fixed in the duodenal bulb with a nitinol anchor, covering 60 cm of duodenum and jejunum. It stays in place for up to 1 year. Repeated implantations are possible. It mimics the Y-roux bypass situation, preventing absorption and separating chyme from bile and pancreatic enzymes. Whether there is also an influence of intestinal hormone release remains a matter of debate [14, 15]. Among all malabsorptive approaches, DJBSs remain the most widely studied devices worldwide.

An earlier meta-analysis including only 2 studies with diabetes concluded that DJBS had an effect on weight loss but not on glycaemic indices [16]. However, a recent meta-analysis including only subjects with obesity and concomitant T2D showed that DJBS clearly improved glycaemic control [17]. This analysis did not include some recent studies with positive [18–20] and one with negative [21] results. The latter, however, included only 34% patients with T2DM and baseline HbA1c was low.

The latest evidence came from the cohort of the German DJBS registry: reduction in HbA1c was significantly higher in the DJBS patients compared to matched controls taken from a cohort receiving standard care (−1.37 vs. −0.51%) [18]. The effect on HbA1c and body weight could be partly preserved over a period of 1-year post explantation [22].

Although most authors of DJBS studies found a positive risk-benefit ratio, potential harm by DJBS must be cautiously considered. In the German registry study, serious adverse events included dislocation and, less frequently, GI bleeding, sleeve obstruction, duodenal ulcer, biliary colic and oesophageal lesions. Of major concern was the incidence of hepatic abscesses. The US ENDO Trial, (ClinicalTrials.gov NCT01728116) was discontinued in 2015 due to a 3.5% incidence of hepatic abscesses, twice as much as in the German registry. Although the trial was stopped early, the results showed clinically significant HbA1c reduction and weight loss for DJBS therapy [23].

Strategies that reduce the rate of abscesses are mandatory. Most of these occurred in months 9–12 after implantation. A shortening of time in situ might therefore be an obvious measure. Most DJBS patients were treated with high-dose proton-pump inhibitors (PPI) to prevent bleeding. It is possible that high stomach pH could favour contamination with bacteria ascending the bile or the blood stream. A reduction of proton-pump inhibitors or a switch to H-1 antagonist would be an alternative option here.

Ongoing studies are hampered by the withdrawal of the EndoBarrier CE Certificate of Conformity. Hopefully this will not stop further prospective studies and lead to a cancellation of this promising principle.

Duodenal Mucosal Resurfacing

This catheter-based procedure applies heat to the duodenal surface using a special balloon (Revita Duodenal mucosal resurfacing [DMR] system [Fractyl Laboratories, Inc., Lexington, KY, USA]). This idea originated from the assumption that the duodenal epithelium plays a pivotal role in mediating insulin resistance, a common

hallmark of the metabolic syndrome. In fact, duodenal mucosa in T2DM exhibits an abnormal mucosal hypertrophy and endocrine hyperplasia, which is the result of a high sugar and fat diet. Thermal ablation is thought to correct this by a stem-cell mediated restoration of normal mucosa [24].

A first proof of principle study was carried out in humans in 39 T2DM patients with promising results. There was a reduction of HbA1c up to 2.5% after 3 months while reducing diabetes medication at the same time [25]. Moreover, serum transaminases normalized after initially increasing, suggesting a beneficial effect on non-alcoholic fatty liver disease.

If this is the result of an altered enteroendocrine cell secretion of products like GLP-1, the change in the gastrointestinal microbiome or bile acid mediated signalling as discussed for other procedures that prevent contact between mucosa, bile and nutrients or simply weight loss remains to be elucidated [26].

Conclusion

Data on glycaemic indices in restrictive procedures remains incomplete. There are some clues that, analogously to operative procedures, a positive effect can be assumed, but this needs to be evaluated further.

The duodenal approaches, DJBS and DMR, appear attractive because of their putative effect on GI hormones.

While DMR remains experimental, there is a robust body of evidence to show that separation of the duodenal passage by DJBS improves metabolic control in patients with T2DM. Due to the non-permanent nature of DJBS it remains to be elucidated if this will translate into a reduction of “hard” endpoints such as cardiovascular events. Further long-term studies are necessary to adopt it as a standard therapy for management of T2DM and obesity. However, since the time the UK Prospective Diabetes Study (UKPDS) was conducted, it is known that there is a sustained benefit after a period of improved glycaemic control, even if followed by a return to usual metabolic control (legacy effect) [27]. Safety issues appear to be manageable; however, they underscore that metabolic endoscopists must be able to provide comprehensive and long-term care to patients with obesity and related T2DM.

Key Points

1. Endoscopic procedures can augment the anti-obesity treatment armamentarium.

2. Currently DJBS is the only procedure with established glycaemic benefit in T2DM patients, presumably with a positive risk-benefit ratio.

3. Other duodenal procedures such as DMR are of particular interest in future research

4. Restrictive procedures have the potential to improve glycaemia in obese T2DM patients but study data is not yet sufficient.

5. The role of ME in standard care of T2DM and obesity is yet to be established.

Disclosure Statement

The author received a single consultant fee from GE Dynamics.

References

- 1 Ginsberg GG, Chand B, Cote GA, Dallal RM, Edmundowicz SA, Nguyen NT, Pryor A, Thompson CC: A pathway to endoscopic bariatric therapies. *Gastrointest Endosc* 2011;74: 943–953.
- 2 Abu Dayyeh BK, Edmundowicz S, Thompson CC: Clinical practice update: expert review on endoscopic bariatric therapies. *Gastroenterology* 2017;152:716–729.
- 3 Popov VB, Ou A, Schulman AR, Thompson CC: The impact of intragastric balloons on obesity-related co-morbidities: a systematic review and meta-analysis. *Am J Gastroenterol* 2017;112:429–439.
- 4 Crea N, Pata G, Della Casa D, Minelli L, Maifredi G, Di Betta E, Mittempergher F: Improvement of metabolic syndrome following intragastric balloon: 1 year follow-up analysis. *Obes Surg* 2009;19:1084–1088.
- 5 Usuy E, Brooks J: Response rates with the spatz3 adjustable balloon. *Obes Surg* 2018;28: 1271–1276.
- 6 Tate CM, Geliebter A: Intragastric balloon treatment for obesity: FDA safety updates. *Adv Ther* 2018;35:1–4.
- 7 Sharaiha RZ, Kumta NA, Saumoy M, Desai AP, Sarkisian AM, Benevenuto A, Tyberg A, Kumar R, Igel L, Verna EC, Schwartz R, Frisora C, Shukla A, Aronne LJ, Kahaleh M: Endoscopic sleeve gastropasty significantly reduces body mass index and metabolic complications in obese patients. *Clin Gastroenterol Hepatol* 2017;15:504–510.
- 8 Huberty V, Ibrahim M, Hiernaux M, Chau A, Dugardeyn S, Deviere J: Safety and feasibility of an endoluminal-suturing device for endoscopic gastric reduction (with video). *Gastrointest Endosc* 2017;85:833–837.
- 9 American Diabetes A: 6. glycemic targets: standards of medical care in diabetes-2018. *Diabetes Care* 2018;41(suppl 1):S55–S64.
- 10 Miller K, Turro R, Greve JW, Bakker CM, Buchwald JN, Espinos JC: MILEPOST Multi-center randomized controlled trial: 12-month weight loss and satiety outcomes after poseSM vs. medical therapy. *Obes Surg* 2017;27:310–322.
- 11 Sullivan S, Swain JM, Woodman G, Antonetti M, De La Cruz-Munoz N, Jonnalagadda SS, Ujiki M, Ikramuddin S, Ponce J, Ryou M, Reynoso J, Chhabra R, Sorenson GB, Clarkston WK, Edmundowicz SA, Eagon JC, Mullady DK, Leslie D, Lavin TE, Thompson CC: Randomized sham-controlled trial evaluating efficacy and safety of endoscopic gastric plication for primary obesity: the ESSENTIAL trial. *Obesity (Silver Spring)* 2017;25: 294–301.
- 12 Thompson CC, Abu Dayyeh BK, Kushner R, Sullivan S, Schorr AB, Amaro A, Apovian CM, Fullum T, Zarrinpar A, Jensen MD, Stein AC, Edmundowicz S, Kahaleh M, Ryou M, Bohning JM, Ginsberg G, Huang C, Tran DD, Glaser JP, Martin JA, Jaffe DL, Farraye FA, Ho SB, Kumar N, Harakal D, Young M, Thomas CE, Shukla AP, Ryan MB, Haas M, Goldsmith H, McCrea J, Aronne LJ: Percutaneous gastrotomy device for the treatment of class II and class III obesity: results of a randomized controlled trial. *Am J Gastroenterol* 2017;112: 447–457.
- 13 Nystrom M, Machytka E, Noren E, Testoni PA, Janssen I, Turro Homedes J, Espinos Perez JC, Turro Arau R: Aspiration therapy as a tool to treat obesity: 1- to 4-year results in a 201-patient multi-center post-market european registry study. *Obes Surg* 2018;28:1860–1868.
- 14 de Jonge C, Rensen SS, Verdam FJ, Vincent RP, Bloom SR, Buurman WA, le Roux CW, Schaper NC, Bouvy ND, Greve JW: Endoscopic duodenal-jejunal bypass liner rapidly improves type 2 diabetes. *Obes Surg* 2013;23: 1354–1360.
- 15 Vilarrasa N, de Gordejuela AG, Casajoana A, Duran X, Toro S, Espinet E, Galvao M, Vendrell J, Lopez-Urdiales R, Perez M, Pujol J: Endobarrier[®] in rade i obese patients with long-standing type 2 diabetes: role of gastrointestinal hormones in glucose metabolism. *Obes Surg* 2017;27:569–577.
- 16 Rohde U, Hedback N, Gluud LL, Vilsboll T, Knop FK: Effect of the endobarrier gastrointestinal liner on obesity and type 2 diabetes: a systematic review and meta-analysis. *Diabetes Obes Metab* 2016;18:300–305.
- 17 Jirapinyo P, Haas AV, Thompson CC: Effect of the duodenal-jejunal bypass liner on glycemic control in patients with type 2 diabetes with obesity: a meta-analysis with secondary analysis on weight loss and hormonal changes. *Diabetes Care* 2018;41:1106–1115.
- 18 Laubner K, Riedel N, Fink K, Holl RW, Welp R, Kempe HP, Lautenbach A, Schlensak M, Stengel R, Eberl T, Dederichs F, Schwacha H, Seufert J, Aberle J: Comparative efficacy and safety of the duodenal-jejunal bypass liner in obese patients with type 2 diabetes mellitus: a case control study. *Diabetes Obes Metab* 2018;20:1868–1877.
- 19 Patel N, Mohanaruban A, Ashrafian H, Le Roux C, Byrne J, Mason J, Hopkins J, Kelly J, Teare J: EndoBarrier[®]: a safe and effective novel treatment for obesity and type 2 diabetes? *Obes Surg* 2018;28:1980–1989.
- 20 van Rijn S, Betzel B, de Jonge C, van Dijk DP, Janssen IM, Berends FJ, Bouvy ND, Greve JW: The effect of 6 and 12 months duodenal-jejunal bypass liner treatment on obesity and type 2 diabetes: a crossover cohort study. *Obes Surg* 2017;28:1255–1262.
- 21 Forner PM, Ramacciotti T, Farey JE, Lord RV: Safety and effectiveness of an endoscopically placed duodenal-jejunal bypass device (EndoBarrier[®]): outcomes in 114 patients. *Obes surg* 2017;27:3306–3313.
- 22 Riedel N, Laubner K, Lautenbach A, Schon G, Schlensak M, Stengel R, Eberl T, Dederichs F, Aberle J, Seufert J: Trends in BMI, glycemic control and obesity-associated comorbidities after explantation of the duodenal-jejunal bypass liner (DJBL). *Obes Surg* 2018;28:2187–2196.
- 23 Kaplan LM, Buse JB, Mullin C, Edmundowicz S, Bass E, Visintainer P, Keating P, Malomo K: EndoBarrier therapy is associated with glycemic improvement, weight loss and safety issues in patients with obesity and type 2 diabetes on oral antihyperglycemic agents. *Diabetes Care* 2016;65(suppl):A326–LB.
- 24 Cherrington AD, Rajagopalan H, Maggs D, Deviere J: Hydrothermal duodenal mucosal resurfacing: role in the treatment of metabolic disease. *Gastrointest Endosc Clin N Am* 2017;27:299–311.
- 25 Rajagopalan H, Cherrington AD, Thompson CC, Kaplan LM, Rubino F, Mingrone G, Becerra P, Rodriguez P, Vignolo P, Caplan J, Rodriguez L, Galvao Neto MP: Endoscopic duodenal mucosal resurfacing for the treatment of type 2 diabetes: 6-month interim analysis from the first-in-human proof-of-concept study. *Diabetes Care* 2016;39:2254–2261.
- 26 Garvey WT: Ablation of the duodenal mucosa as a strategy for glycemic control in type 2 diabetes: role of nutrient signaling or simple weight loss. *Diabetes care* 2016;39:2108–2110.
- 27 Chalmers J, Cooper ME: UKPDS and the legacy effect. *N Engl j med* 2008;359:1618–1620.