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REVIEW

Surgical cure for type 2 diabetes by foregut or hindgut operations: a myth or reality? A systematic review

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Abstract

Background Bariatric surgery results in remission of type 2 diabetes mellitus in a significant proportion of patients. Animal research has proposed the foregut and hindgut hypotheses as possible mechanisms of remission of T2DM independent of weight loss. These hypotheses have formed the basis of investigational procedures designed to treat T2DM in non-obese (in addition to obese) patients. The aim of this study was to review the procedures that utilise the foregut and hindgut hypotheses to treat T2DM in humans.

Methods A systematic review was conducted to identify the investigational procedures performed in humans that are based on the foregut and hindgut hypotheses and then to assess their outcomes.

Results Twenty-four studies reported novel procedures to treat T2DM in humans; only ten utilised glycated haemoglobin A1c (HbA1c) in their definition of remission. Reported remission rates were 20–40 % for duodenal–jejunal bypass (DJB), 73–93 % for duodenal–jejunal bypass with sleeve gastrectomy (DJB-SG), 62.5–100 % for duodenal–jejunal bypass sleeve (DJBS) and 47–95.7 % for ileal interposition with sleeve gastrectomy (II-SG). When using a predetermined level of HbA1c to define remission, the remission rates were lower (27, 63, 0 and 65 %) for DJB, DJB-SG, DJBS and II-SG.

Conclusions The outcomes of the foregut- and hindgut-based procedures are not better than the outcomes of just one of their components, namely sleeve gastrectomy. The complexity of these procedures in addition to their comparable outcomes to a simpler operation questions their utility.

Keywords Foregut theory · Hindgut theory · Remission ot type 2 diabetes

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Since the publication of the first report by Pories et al. [1] showing remission of type 2 diabetes mellitus (T2DM) after surgery, conventional bariatric procedures have shown benefit in controlling T2DM in patients with BMI >35 kg/m^2. The mechanisms proposed for remission of diabetes are generally classified into weight loss dependent and non-weight loss dependent [2].

The improvement in control of T2DM after purely restrictive procedures such as laparoscopic adjustable gastric banding (LAGB) is largely dependent on and proportional to weight loss [3]. However, the case for weight loss-independent mechanisms is strong and based on three observations: firstly, rapid improvement in diabetes after certain types of bariatric surgery [4]; secondly, greater diabetic improvement after certain types of bariatric surgery than with equivalent weight loss from other interventions [5–8]; thirdly, cases of late hyperinsulinaemic hypoglycaemia [2].

Based on these observations, several mechanisms have been proposed to explain the weight-independent improvement and remission of diabetes after bariatric and metabolic surgery. It is postulated that bariatric surgery works through modulation of bile acids, gut microbiota or incretins to alter weight and/or insulin sensitivity. The most popular hypotheses continue to be the foregut and hindgut theories based on modulation of incretins. Both theories are strongly supported by evidence from animal studies [9, 10]. The foregut theory proposes that food bypassing the duodenum leads to a decrease in unknown anti-incretin hormones which leads to improved insulin sensitivity [11, 12]. The hindgut theory states that early exposure of undigested food to the hindgut leads to increased secretion of incretins with subsequent improvement in glycaemic control [13, 14].

New surgical procedures have been designed on the basis of these theories to achieve glycaemic control in non-obese T2DM patients whilst reducing morbidity and exerting a minimal effect on weight.

This article aims to systematically review the literature describing these investigational surgeries designed to treat T2DM in obese as well as the 'non-morbidly obese'. The study evaluates the usefulness and validity of the 'foregut' and 'hindgut' hypotheses in improving glycaemic control.

Materials and methods

A two-stage systematic review of the literature was performed. The first stage aimed to identify investigational procedures based on the foregut or hindgut theories. The second stage ascertained outcomes of these operations in humans with emphasis on their outcomes in the treatment of T2DM. Using the National Health Service (NHS) evidence advanced search facility (HDAS), we searched PubMed, MEDLINE, Embase, CINAHL, British Nursing Index and AMED. The first stage of the search included the following terms: (foregut or hindgut) and diabetes. After identifying the relevant procedures, we searched the same databases for these procedures. There was no time limit on the search. The inclusion criteria are as follows: procedures based on the foregut and hindgut theories, human studies, articles written in the English language, no duplication of data. Exclusion criteria used in this study are animal studies, conference abstracts, articles not written in the English language, short-term objectives, review articles and duplication of data.

Two authors reviewed the abstracts independently. A full-text article for each relevant article was obtained, and manual cross-referencing from the bibliography was performed to ensure inclusion of all of the relevant related literature. Following this, relevant data were extracted from each paper. The data extracted are study design, procedures included in the study, inclusion criteria, successful implant, number of patients with T2DM, number of patients with T2DM completing follow-up, follow-up, baseline mean body mass index (BMI) kg/m^2, follow-up mean BMI kg/m^2, percentage excess weight loss, pre- and post-operative fasting glucose (mg/dl), pre- and post-operative HbA1c, definition of remission of diabetes in the paper and remission rate.

Blood glucose is expressed in the conventional units (mg/dl) for simplicity of comparison and where necessary has been converted from SI units (mmol/l) by multiplying it by the conversion factor 18.

The World Health Organization (WHO) classification of obesity was used to improve uniformity in comparing studies [15]. BMI cut-off points of 23, 27.5, 32.5 and 37.5 kg/m^2 (corresponding to BMI 25, 30, 35 and 40 of the WHO classification) have been added as points for the Asian population [16].

The American Diabetes Association's [17] definitions of remission of T2DM are used in the manuscript. Partial remission is HbA1c <6.5 %, fasting glucose 100–125 mg/dl (5.6–6.9 mmol/l)of at least 1 year's duration in the absence of active pharmacological therapy. Complete remission is a return to 'normal' measures of glucose metabolism (HbA1c in the normal range, fasting glucose <100 mg/dl or 5.6 mmol/l)of at least 1 year's duration in the absence of active pharmacological therapy.

Results

Data retrieval

The initial literature search identified a total of 293 papers for screening. After electronic and manual de-duplication, 177 papers were identified. Of these, 146 papers were excluded after review of the abstracts. The remaining 31 papers were fully reviewed. Subsequently, seven papers were excluded due to duplication of data and a further four papers were excluded as they were found to be reviews with no extra original data. After manual cross-referencing, no new papers were identified that met the inclusion criteria. Finally, 24 papers were included in this systematic review. Figure 1 shows a flow diagram of the review process.

Three types of surgical procedures that utilised the principles of the foregut and hindgut theory to treat T2DM in humans were identified which are duodenal–jejunal bypass (DJB), duodenal–jejunal bypass with sleeve gastrectomy (DJB-SG), endoscopic DJB sleeve (DJBS), ileal interposition with sleeve gastrectomy (II-SG).

A total of 24 papers were included that offered a novel surgery to a total of 921 patients with T2DM (Fig. 1).

Systematic review of the procedures

Duodenal–jejunal bypass (Fig. 2)

Technical details

The duodenum is transected 1–2 cm below the pylorus, and the jejunum is transected 50 cm from the ligament of Treitz. The distal end of the jejunum is anastomosed end-

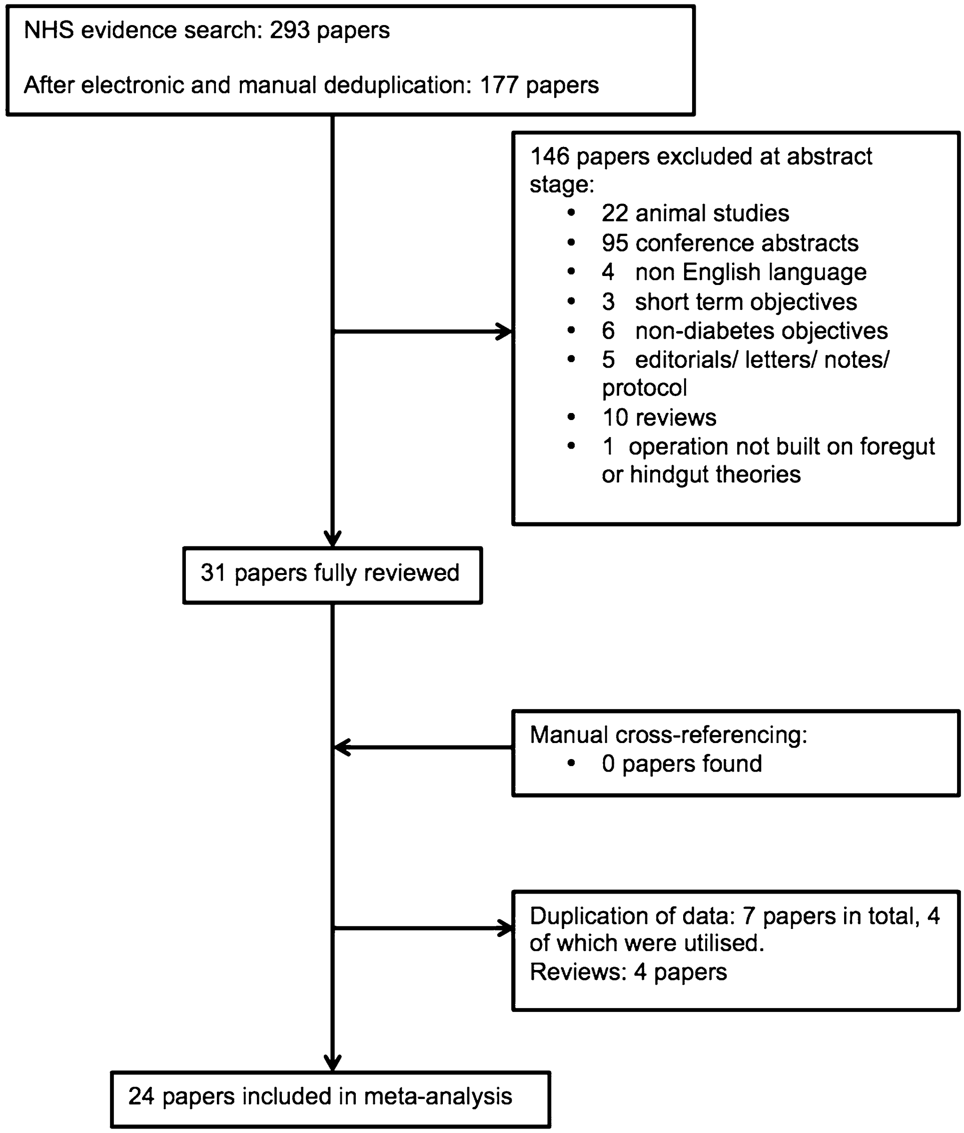

Fig. 1 PRISMA flow diagram

to-end to the duodenum and the proximal end is anastomosed end-to-side to the jejunum, 80 cm from the duodenojejunostomy. SG is added to this operation in some studies.

Morbidity and mortality

One death secondary to pulmonary embolism [18] and one major post-operative complication in the form of stricture of gastric tube [19] were reported. This was treated with stricturoplasty.

Transient post-operative nausea and vomiting were the most commonly reported minor complications ranging from 20 to 42 % [18, 20, 21] Other rare complications were marginal ulcer, ileus, pancreatitis and late bowel obstruction.

Outcomes of glycaemic control

In nine small studies, 123 patients (all diabetic and BMI <35 kg/m^2) underwent DJB and 60 had DJB-SG (48 were diabetic and had BMI >32 kg/m^2 as per Asian guidelines for bariatric surgery). Following DJB, reported diabetes remission rate was between 16 and 100 % (see Table 1). Diabetes remission rate was 73–91 % after DJB-SG. When using the more universally acceptable definition of remission, the remission rate was 27 % in DJB and 63 % in DJB-SG (Table 2).

Only one study reported a fall in HbA1c within 1 month [22]. The rest of the studies reported remission at 6 months or later making it difficult to confirm whether it was independent of or secondary to weight loss.

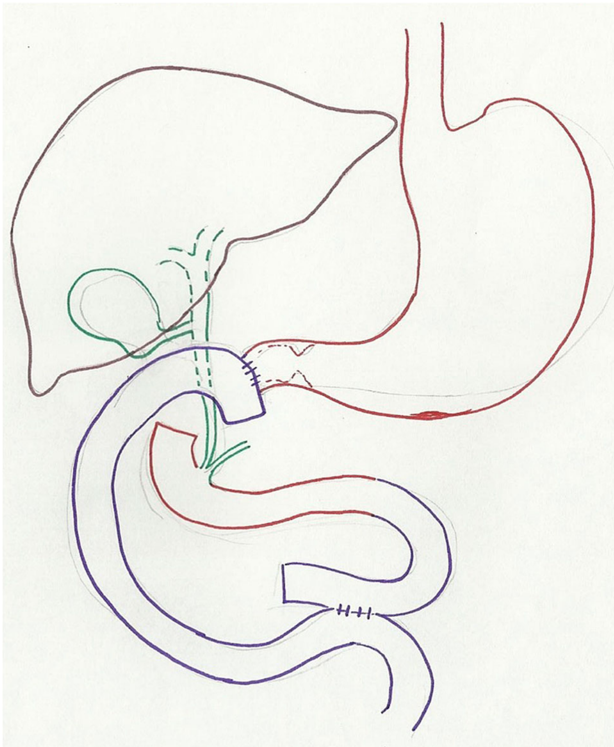

Fig. 2 Duodenal–jejunal bypass (DJB) with or without sleeve gastrectomy (DJB-SG)

Endoscopic DJB sleeve (Fig. 3)

Technical details

The DJBS is a single-use endoscopic device, deployed under radiological guidance. The device is composed of tiny nitinol lateral barbs for anchoring and an impermeable plastic conduit that prevents contact of the chyme with bile–pancreatic secretions up to the proximal jejunum. The procedure is performed under general anaesthesia. The device is introduced over a guide wire, and the plastic conduit is stretched to overlay the duodenum and the proximal region of the jejunum. After correct positioning, the anchoring system is freed setting the device in the duodenal bulb. A contrast study is performed to verify the position of device and to rule out obstruction within the plastic conduit.

Morbidity and mortality

No major morbidity or mortality is reported in any of the studies performed. Reported procedure-related minor complications include upper abdominal pain, nausea, vomiting, flatulence, oesophagitis, gastritis, erosive duodenitis, constipation, diarrhoea.

Outcomes of glycaemic control

A total of 180 patients with T2DM were described in nine articles. All of the studies included patients with an average BMI >30 kg/m^2. The remission rate of diabetes was 62.5–100 % (Table 3). One small study defined remission as normalisation of fasting plasma glucose or HbA1c and no ADM. This study showed a remission rate of 75 % ($n = 4$) [23]. This study, however, did not define the level of HbA1c that was considered to be normal. It was therefore impossible to discern whether there was a significant difference in regards to remission of diabetes between the gastro-duodenojejunal sleeve (starting at gastro-oesophageal junction) and DJB sleeves due to different definitions of remission of diabetes. The rate of remission of diabetes after insertion of endoscopic sleeves was assessed regularly in three studies [23–25]. Two of these three studies reported remission of diabetes within one week [24, 25]. One study showed remission of diabetes within 24 h. These changes do not seem to be associated with weight loss [23].

None of the studies that performed DJBS used 'predetermined HbA1c level and no ADM' as the remission criteria. We were unable to provide a synthesised or non-synthesised remission rate after DJBS.

Ileal interposition (Fig. 4)

Technical details

After performing SG, devascularisation of the greater curvature of the stomach is continued to the duodenum 3–4 cm beyond the pylorus. Two techniques were used. The first is ileal interposition with diverting SG. The duodenum is transected using a 60-mm linear stapler. The proximal cut end is delivered in the infracolic compartment through a mesenteric window in the transverse mesocolon. An ileal segment of 150 cm is created 50 cm proximal to the ileocecal valve. This segment is anastomosed peristaltically to the delivered first portion of the duodenum. The jejunum at 50 cm from the ligament of Treitz is anastomosed to the distal end of the interposed ileum.

The second technique is ileal interposition with SG (non-diverting). The ileal segment is created as above. This segment is then interposed in the jejunum 30 cm from the ligament of Treitz.

Morbidity and mortality

Early (0.99 %) and late (1 %) mortality is reported by DePaula et al. [26]. Acute renal failure and dehiscence of Meckel's diverticulectomy were the causes of early mortality. Late mortality was related to intestinal obstruction and Guillian–Barre syndrome secondary to advanced renal

Table 1 Duodenal–jejunal bypass table

Author/year	Study design	Procedures included	Inclusion criteria (BMI kg/m^2 and T2DM)	Total number	Number T2DM	Number T2DM completing follow-up	Follow-up (months)	Baseline mean BMI kg/m^2	Follow-up mean BMI kg/m^2
Duodenal–jejunal bypass (DJB)									
Cohen [32]	Case report	DJB	29–30.3	2	NA	NA	9	29.6	28
Ramos [34]	Prospective study	DJB	>20 and <30, T2DM 2–8 years, not on insulin	20	20	20	6	27.1	24.4
Ferzli [33]	Prospective trial	DJB	<35 with T2DM	7	7	7	12	27.5	27.28
Lee [22]	Prospective cohort study	DJB	<30, T2DM for ≤10 years	6	6	5	6	25.25	NA
Cohen [18]	Prospective study	DJB	<30	35	35	35	12		
Klein [20]	Prospective trial	DJB	23.0–34.0, T2DM <10 years, HbA1c >7.5 %	35	35	35	12	27.0	25.9
Geloneze [21]	Case matched study	DJB	T2DM treated with Insulin <5 years, diagnosed <15 years. HbA1c 7.5–10 %	18	18	18	12 months	26.1	26.4
Duodenal–jejunal bypass with sleeve gastrectomy (DJB with SG)									
Raj [39]	Prospective case series	DJB with SG	Bariatric surgery guidelines[a]	38	26	26	17 (12–27)	42.3	30.2
Huang [19]	Prospective	Loop DJB with SG	18–65 yo with poorly controlled T2 DM for at least 6/12 and HbA1c ≤7	22	22	22	6	28.4	23.4

Author/year	% Excess weight loss	Pre-op fasting glucose (mg/dl)	Post-op fasting glucose (mg/dl)	Pre-op HbA1c	Post-op HbA1c	Definition of remission	Remission rate (%)	Time to reach remission	Proportional to weight loss?
Duodenal–jejunal bypass (DJB)									
Cohen [32]	NA	NA	83	NA	5.35	Free of ADM	100		
Ramos [34]	7.8	171.3	96.3	8.8	6.8	Free of ADM	90	Not stated	Not stated
Ferzli [33]	NA	209	154	9.4	8.5	Reduced ADM, improved HbA1c	71.4	HbA1c worse at 1 week in 5 In 1 year 5 achieved remission	BMI assessed at 1 year
Lee [22]	NA	NA	NA	8.1	7.4	Reduced requirement of ADM	100	HbA1c fall within month 1	weight fall of 5.6 kg (average) in month 1
Cohen [18]						HbA1c <7 % and free of ADM	40	Not stated Assessed at 12 months	Assessed at 12 months
Klein [20]	4.2	188	175	9.3	7.7	HbA1c <6.5 % and free of ADM	20	Unclear	
Geloneze [21]	NA	9.9	8.3	8.9	8	HbA1c <7 % with or without meds	16 %	Assessed at 12 months	
Duodenal–jejunal bypass with sleeve gastrectomy (DJB with SG)									
Raj [39]	71.84	NA	NA	NA	NA	HbA1c <7 and free of ADM	73	No timeframe	Not stated
Huang [19]		147	110	8.6	6.2	Fasting glucose <100 HbA1c <6 with no oral hypoglycaemics or insulin	91	6 months	Not stated

EBMI excess body mass index, *ADM* anti-diabetic medication, *SG* sleeve gastrectomy, *DJB* duodenal–jejunal bypass, *IGT* impaired glucose tolerance

No set criteria to define resolution; possibly, these patients were free of anti-diabetic medication

Figures in bracket are for control group

[a] Asian guideline recommend bariatric surgery for people with BMI >37 or >32 with medical co morbidities

Table 2 Remission rates after DJB and DJB-SG in studies utilising levels lower than predetermined level of HbA1c and freedom of ADMs as the definition of remission

DJB studies with predetermined HbA1c level and no ADM as the remission criteria	Number of T2DM patients	Number of patients who had remission	Remission rate (%)
DJB studies			
Cohen [18]	35	14	40
Klein [20]	35	7	20
Geloneze [21]	18	3	16
Total	**88**	**24**	**27**
DJB-SG studies			
Raj [39]	26	19	73
Huang [19]	22	11	50
Total	**48**	**30**	**63**

disease. In the same series, authors report 2.5 % reoperation rate, 8.4 % early major complications (pneumonia, ileus, gastrointestinal bleeding, myocardial infarction, acute renal failure, cardiac arrhythmia, intra-abdominal abscess, urinary tract infection) and 3.5 % late major complications (vomiting, abdominal wall infection, intra-abdominal bleeding, intestinal obstruction, stricture of gastric tube). In their previous study, the authors reported 5 (7.3 %) major complications, namely fistula requiring reoperation ($n = 1$), GI bleed ($n = 1$), urinary tract infection ($n = 1$), pneumonia ($n = 2$) [27]. No major morbidity or mortality is reported by any other group.

Outcomes of glycaemic control

Six studies have reported II-SG on 474 patients, 381 of which were diabetic [26–31]. The studies reported variable success rates of 47–95.7 % for T2DM remission (Table 4). When using the more universally acceptable definition of remission (predetermined HbA1c level at least <7 with no use of ADMs), the cumulative remission rate was 77.8 % (Table 5).

Review of study characteristics and variables

Demographic and types of studies

Of the 24 articles, 15 of these studies were based in South America and the other studies were based in other parts of the world, North America, Netherlands, India, China and Korea. Two of the studies were randomised controlled trials, five were non-randomised controlled trials or series with comparison groups, 16 were case studies, and one article was a case report. All of the studies were conducted at single centres ($n = 23$) except for one which was a multicentre study.

BMI range

The authors of 11 articles offered surgery to patients with a BMI less than 35 kg/m^2 [18, 20–22, 26, 27, 29, 31–34], and the authors of 7 articles offered surgery to patients with a BMI greater than 35 kg/m^2 [23, 24, 28, 35–38].

One study offered surgery to obesity class II as defined for Asian populations (i.e. BMI >37 kg/m^2). The rest of the studies offered surgery to different ranges of BMI above and below 35 kg/m^2 [19, 25, 30, 39–41].

DJB was offered to patients with a BMI of <35 kg/m^2, and DJB-SG was offered to patients with a larger BMI range from 21.8 to 45 kg/m^2. DJBS was offered to patients with BMI >35 kg/m^2, apart from one study where patients with BMI >26 kg/m^2 were offered surgery [40]. II-SG was offered mainly to patients whose BMI was <35 kg/m^2 (four papers) [26, 27, 29, 31]. One study offered surgery to patients with BMI >35 kg/m^2 [28] and one study offered surgery to patients with BMIs above and below 35 kg/m^2 [30].

Definition of remission

Two articles defined remission of diabetes as HbA1c <6 % and fasting glucose <100 mg/dl for at least 1-year duration without the use of pharmacological therapy [19, 28]. Three articles defined remission as HbA1c <6.5 % and absence of anti-diabetic medications (ADMs) [20, 29, 31], and four articles defined remission as HbA1c <7 % with patients being free of ADMs [18, 19, 27, 30, 39].

Other articles defined remission as normal fasting plasma glucose, HbA1c and no ADM without explicitly providing the numeric values of normal levels (one article) [23], HbA1c <7 % (two articles) [35, 36], HbA1c <7 % with or without ADM (one article) [21], HbA1c <6.5 % (one article) [26], no ADM (three articles) [32, 34, 38] and improved glycaemic control (six articles) [22, 24, 25, 33,

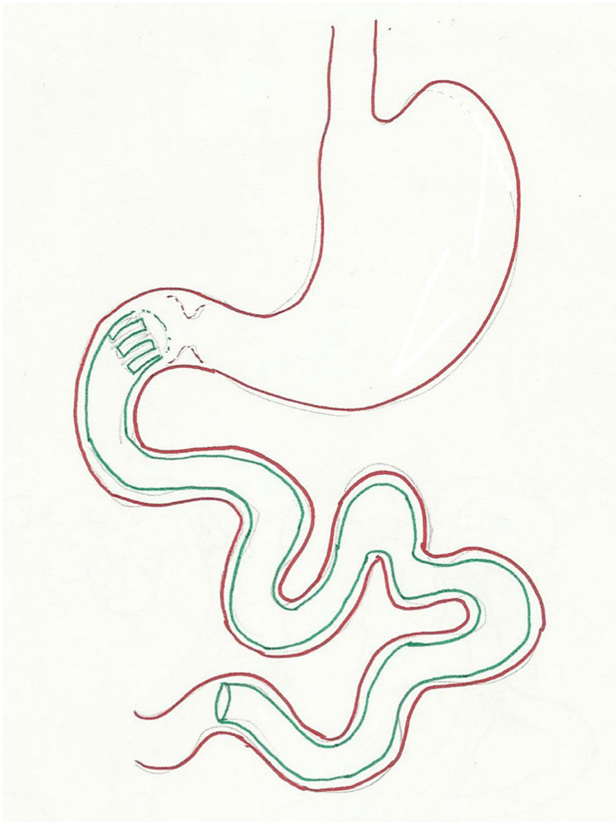

Fig. 3 Endoscopic DJB sleeve (DJBS)

37, 40]. One article reported no clear endpoint for remission of diabetes [41].

Length of follow-up

Nine studies had follow-up lengths of less than or equal to 6 months [19, 22–25, 34, 36, 38, 41]. Of these, three studies had follow-up periods of 3 months [23, 24, 38] and one had a follow-up period of 5 months [41]. Some of the studies that performed DJB and DJBS had follow-up periods of 6 months or less. Studies where II-SG was performed had follow-up periods of a minimum of 9 months and a maximum follow-up period of 39.1 months.

There were a total of 13 studies with a follow-up of greater than 12 months. Of these, DJB was performed in five of these studies [18, 20, 21, 33, 39]. DJBS performed in three studies [35, 37, 40] and II-SG performed in five studies [26–29, 31].

Discussion

Foregut and hindgut procedures based on animal studies to date have shown limited and potentially promising success in the control of T2DM [9, 12, 42–44]. There is, however, no convincing evidence of its success in larger mammals or primates. Hence, the use of these theory-based procedures in humans at this juncture may be premature due to its lack of evidence in successfully achieving remission of T2DM.

In an effort to explain the weight loss-independent mechanisms of remission of T2DM, these theory-based procedures performed in humans seem to be a simplistic account of more complex physiological and chemical alterations that occur during the ingestion, storage, transit and digestion of food in the human body. It is well hypothesised that a combination of hormones for example incretin, glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic polypeptide can alter in the post-prandial period [14, 44]. Other studies have suggested an alteration in the levels of ghrelin, peptide YY and leptin that play an important part in the maintenance of glucose homoeostasis and alterations in weight [45, 46]. Aside from the chemical alterations that occur in patients following bariatric surgery, these procedures seemingly avoid the acknowledgement of the physiological mechanisms involved in digestion of food for example rate of gastric emptying, constitution of meals, absorptive capacities of the different segments and the different transit times from one part of the ileum to another in different patients [47–51]. Appreciation of these physiological mechanisms is not reflected in studies as demonstrated by the variation in length of the excluded duodenojejunal limb [27, 28] and the use of diverting/non-diverting sleeve gastrectomy with II [26].

This systematic review highlights a wide variation in the key areas of the reported series. It also highlights several key messages.

The lack of standardisation of these procedures and the wide variation in definitions of remission of T2DM [17] make direct comparisons between the studies difficult. In most of these studies, the number of patients and length of follow-up played a huge negative impact on the final outcome and reliability of these studies. This precludes procedure-specific conclusions despite our systematic review. It is clear in this systematic review article that a combination of conventional and theory-based procedures (e.g. SG in DJB-SG and II-SG and endoscopic sleeve starting at the oesophagus in DJBS) produced seemingly promising results. Hence, this begs the question whether the effect of these procedures in achieving remission of T2DM is related to the SG (conventional bariatric procedure) or to the theory-based procedure components of the operation.

In an attempt to overcome some of the above issues and give readers and researchers a reasonable, albeit imperfect view of the outcomes of these procedures, we synthesised the data from the studies that reported an acceptable definition of remission of diabetes mellitus and produced an overall remission rate of diabetes for each procedure (Tables 2, 5).

Table 3 Duodenal–jejunal sleeve table

Author/year	Study design	Procedures included	Inclusion criteria (BMI kg/m^2 and T2DM)	Successful implant/total number	Number T2DM	Number T2DM completing follow-up	Follow-up (months)	Baseline mean BMI kg/m^2	Follow-up mean BMI kg/m^2
Rodriguez-Grunert [23]	Prospective open label	Endoscopic DJBS	Those for LRYGB placed pre-op for 12 weeks	12	4	10/12 and 4/4	3	43	38.7
Rodriguez [25]	Randomised, single blind, sham-controlled, trial	Endoscopic DJBS/sham	30–50, T2DM for 10 years, HbA1c >7 % and <10 %	12 DJBS versus 6 sham endoscopy	12/6	10/4	6	38.9	NA
Schouten [24]	Multicentre randomised control trial	Endoscopic DJBS versus control	Those for LRYGB, <60 BMI	30 (11 diet controlled)	8	8	3	48.9	43.4
DeMoura [36]	Prospective case series	Endoscopic DJBS	BMI ≥35 kg/m^2 with T2DM	78/81 successful implanted	78	54 (TG/HDL >3.5)	6	43.8	
dler [38]	Prospective single-centre trial	Endoscopic Gastro-jejunal bypass,	Bariatric criteria	17/22	7	7	3	42	
Escalona [37]	Single arm, open label, prospective trial	Endoscopic DJBS	>35	39/42	6	6, 24/39	12	43.7	
DeMoura [35]	Prospective open label clinical trial	Endoscopic DJBS	40–60	22	22	13	12	44.8	−6.7[a]
DeJonge [41]	Prospective case series	Endoscopic DJBS	BMI 30–50 and T2 DM <10 years. HbA1c 7.5–10 %	17	17	17	5	37	
Cohen [40]	Prospective open label clinical study	Endoscopic DJBS	T2DM of >10 years (HbA1c) >7.5 % and >10 % and BMI >26 to <50 kg/m^2	20/20	20	16	12	30	28.5

Author/year	% Excess weight loss	Pre-op fasting Glucose (mg/dl)	Post-op fasting Glucose (mg/dl)	Pre-op HbA1c	Post-op HbA1c	Definition of remission	Remission rate (%)	Time to reach remission	Proportional to weight loss?
Rodriguez-Grunert [23]	23.6	NA	NA	NA	NA	Normal FPG, HbA1c and No ADM	75	Within 24 h	No
Rodriguez [25]	−10.2 kg weight change	195	−83[a]	9.1	−2.4[a]	Improvement in FPG and 7 point glucose profile	100	1 week	Not stated
Schouten [24]	19	199.8	167.4	8.8	7.7	Lower FPG, HbA1c and ADM	87.5	6 of 8 fall in ADM/insulin in 1 week	No
DeMoura [36]	12.6 % loss of initial weight	NA	NA	NA	NA	HbA1c <7 %	70.3	Not stated	Not stated
dler [38]	39.7	NA	NA	NA	NA	No anti-diabetic medication	100+	Time to remission not stated	Unclear if proportional
Escalona [37]	47.0	104	94	6.3 %	6 %	Improved glycaemic control	100	Not stated	Not stated
DeMoura [35]	35.5	179.4	−37.1[a]	8.9	−2.3[a]	HbA1c <7 %	73	Fall in FPG within week 1 HbA1c <7 by week 52	Not stated
DeJonge [41]	29.8	11.6	8.6	8.4	7	NA	NA	Fall in fasting glucose in 1 week	Not stated
Cohen [40]	Decrease by 6.5 kg	207	155	8.7	7.5	HbA1c with medications	62.5 %	<7 HbA1c at week 12	Y

[a] Change in value *NA* not available, *EBMI* excess body mass index, *ADM* anti-diabetic medication, *FPG* fasting plasma glucose, *DJBS* endoscopic DJB sleeve

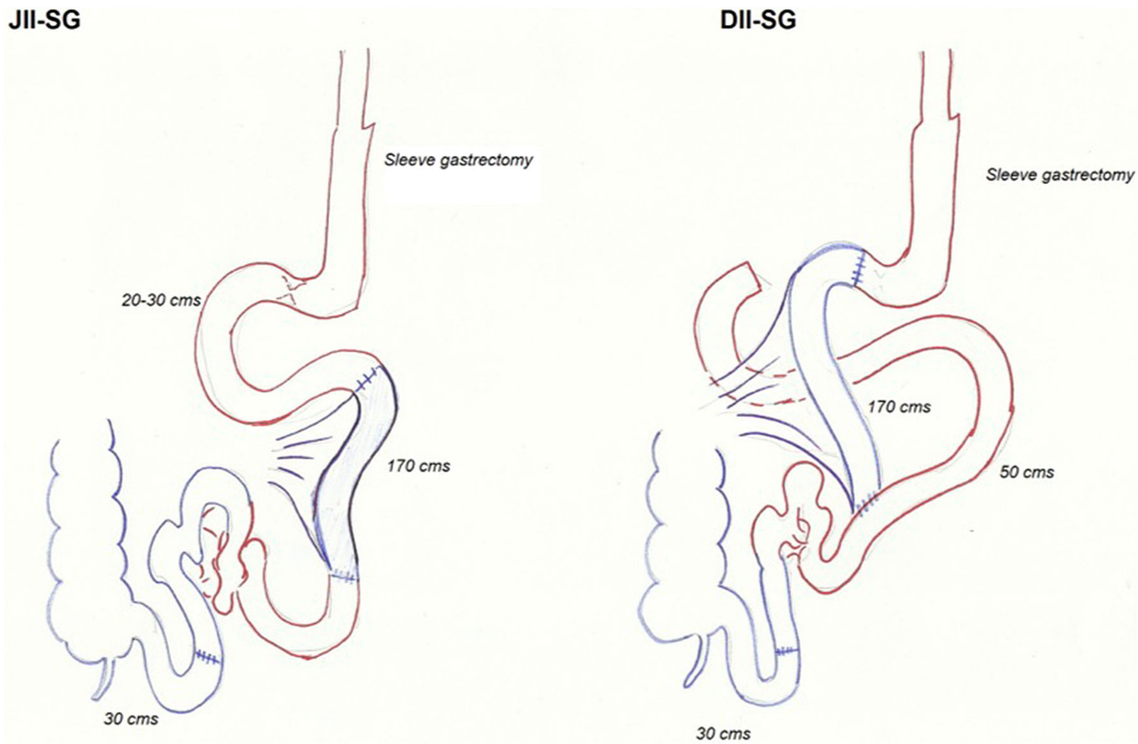

Fig. 4 Ileal interposition (II) with sleeve gastrectomy

Current conventional bariatric procedures have been shown in the longer term to have produced better results than these theory-based procedures [4]. A meta-analysis of metabolic and bariatric surgery for morbidly obese patients showed greater than 78.1 % of diabetic patients who had complete resolution with improvement in control or resolution of diabetes in 86.6 % of patients [4]. The same conventional surgery on patients with BMI <35 kg/m^2 has shown adequate diabetic control (HbA1c <7 % and no diabetes medications) in 80–90 % of patients, along with a BMI loss of 5–7.5 % [52–54].

In randomised and non-randomised studies, SG alone achieved high rates of remission of diabetes [53, 55, 56]. A systematic review by Gill et al. assessing the improvement in control of T2DM in obese patients following SG showed resolution of T2DM in 66.2 % of patients, with improvement in control of T2DM in 26.9 % of patients [57]. These results are comparable to combined procedures identified in this review, where DJB-SG and II-SG achieved overall remission rates of 63 and 77.8 %, respectively (Table 6). Indeed the only procedure identified in the literature that is solely based on the foregut theory is the DJB which is shown to achieve remission rates of T2DM of 27 %, suggesting that the SG component in these theory-based combination procedures plays a more significant role in remission of T2DM.

Data on the complexity of the operation (using number of anastomoses as a surrogate marker of complexity), morbidity, mortality and diabetes resolution are presented in Table 6 and compared with SG and other conventional bariatric procedures. It clearly shows lack of benefit of these theory-based procedures alone, and we therefore question the need to combine additional procedures to conventional bariatric operations as each procedure is fraught with increased complexity, mortality and morbidity. Gagner et al. [58] suggested that simpler procedures for example SG should be performed initially (with 85 % resolution of T2DM) before considering the addition of other procedures such as II or DJB to further improve glycaemic control.

Mortality associated with conventional Roux-en-Y gastric bypass (RYGB) surgery has been reported in studies to be 0.4–0.5 % [59, 60]. Meanwhile morbidity associated with RYGB surgery has been reported to have complication rates of approximately 8.4 % for early major complications (including pneumonia and gastro-jejunal leaks) [60]. Another study reported 3.3 % major complication rates after RYGB, of which small bowel obstruction rates were 1.1 % [59]. Anastomotic leak rates reported in the literature were 0.37–3 % [59, 61]. In contrast to this, the DJB and DJBS procedures highlighted in this systematic review report no mortality [19, 34] and II studies report early mortality rates of 0.99 % and later mortality rates of 1 % [26]. Meanwhile, major complications of anastomotic leak and bowel obstruction following DJB were reported to be 0.8–1.3 % [26, 28] and 0.8–3.3 %, respectively [26, 28, 31].

Table 4 Ileal interposition table

Author/year	Study design	Procedures included	Inclusion criteria (BMI kg/m^2 and T2DM)	Successful implant/Total number	Number T2DM	Number T2DM completing follow-up	Follow-up (months)	Baseline mean BMI kg/m^2	F/u mean BMI kg/m^2
DePaula [27]	Prospective case study	Il + SG[a]	21–29 T2DM >3 years	69	69	69	21.7	25.7	21.8
Kumar [30]	Prospective case study	Il + SG[b]	25–45, T2DM for 3 years +HbA1c >8 %	10	5 [5]	10	9.1	33.1 (34.5) [c]	24.6 (27.9)[c]
Tinoco [31]	Prospective case study	Il + SG[b]	No BMI criteria, T2DM for 3 years +	30	30	30	13	30.8	25.7
DePaula [26]	Retrospective review of database	II + SG JII-SG AND DII-SG	<35 minimum 2 year FU T2DM	202	202	202	39.1	29.7	23.5
Kota [29]	Prospective case study	Il + SG[b]	>18.5	43	43	42	20.2	33.2	26.6
DePaula [28]	Retrospective analysis	LII-SG	BMI >40 or ≥35 with comorbidities	120	8 + 19 [27]		38.4	43.4	25.7

Author/year	% Excess weight loss	Pre-op fasting Glucose (mg/dl)	Post-op fasting Glucose (mg/dl)	Pre-op HbA1c	Post-op HbA1c	Definition of remission	Remission rate (%)	Time to reach remission	Proportional to weight loss?
DePaula [27]	21.8–29.2 kg/m^2 BMI loss	218	102	8.7	5.9	HbA1c <7 % and free of all ADM	95.7	31.9 % normalisation of FPG within 2 weeks	Not stated
Kumar [30]	15–30 %	208.4 (196.6)[c]	97.8 (134.2)	10.9 (9.2)[c]	6.1 (7.3)[c]	HbA1c <7 % and free of all ADM	70	Within f/u time of 13.6 months	Not stated
Tinoco [31]	NA	201	99.6	9.5	6.2	HbA1c <6.5 % and free of all ADM	80	Within f/u time average 13 months	Not stated
DePaula [26]	22.5 % weight loss	202.1	112.2	8.7	6.2 % (JII-SG) 5.9 (DII-SG)	HbA1c <6.5 %	78.3	Within f/u time	Not stated
Kota [29]	25 % reduction in BMI	184.8	119.6	9.6	7.2	HbA1c <6.5 % and free of all ADM	47	Not stated	Not stated
DePaula [28]	84.5	291.7	99.8	8.6	5.9	HbA1c <6 % and fasting plasma glucose <100 for 1 year with no ADM	68.4	Not stated	Not stated

NA not available, *ADM* anti-diabetic medication, *SG* sleeve gastrectomy, *II* ileal interposition

[a] 170 cm of ileum up to the first portion of the sectioned duodenum

[b] 170 cm ileum 30 cms from ileocaecal junction and 20–50 cm from duodenojejunal flexure

[c] Values in bracket are for those with <10-month follow-up

Table 5 Remission rates after II-SG in studies utilising levels lower than predetermined level of HbA1c and freedom of ADMs as the definition of remission

Ileal interposition with sleeve gastrectomy studies with predetermined HbA1c level and no ADM as remission criteria.	Number of T2DM patients	Number of patients who had remission	Remission rate (%)
DePaula [27]	69	66	95.7
Kumar [30]	10	7	70
Tinoco [31]	30	24	80
Kota [29]	43	20	47
DePaula [28]	19	16	68.4
Total	**171**	**133**	**77.8**

Table 6 Comparison of new procedures, sleeve gastrectomy and other conventional bariatric procedures with the total number of surgeries performed, total number of anastomosis, mortality, major morbidity and remission of T2DM

Procedure	Total number of procedures performed	Number of anastomoses	Mortality	Major morbidity	T2DM remission
New procedures					
Duodenal–jejunal bypass	123	2	1 (0.8 %)	0	24/88 (27 %)
Duodenal–jejunal bypass sleeve	60	2	0	1 (1.6 %)	30/48 (63 %)
Duodenojejunal sleeve	169	0	0	0	
Ileal interposition with sleeve	474	3	2 (0.4 %)	17 (3.5 %)	133/177 (77.8 %)
Sleeve gastrectomy [57]	**1117**	**0**	**4 (0.36 %)**	**45 (4.03 %)**	**66.2 %**
Other conventional bariatric procedures [4]					
BPD or duodenal switch	3030	2	1.1 %	NA	282/288 (97.9 %)
Roux-en-Y gastric bypass	5644	2	0.5 %	NA	829/989 (83.8 %)
Gastric band	2297	0	0.1 %	NA	98/205 (47.8 %)

Number of anastomoses used as surrogate marker for complexity of the procedure

Remission for those with predetermined acceptable criteria for remission

There are several limitations to this review article, some of which has been described above. One other factor that limits our conclusions following this systematic review is the length of follow-up. Whilst we had tried to include studies with longer follow-up periods, the poverty of data and available studies published in the English-speaking world on these theory-based procedures meant that the follow-up period assessed in this systematic review was shorter than the ideal follow-up period the authors of this study would have liked to achieve.

Conclusion

Foregut, hindgut or sleeve?

The only operation that is based on the foregut theory and applied in humans is DJB (without sleeve). The rest of the operations include additional 'non-theory' elements such as SG. The remission rate for DJB alone (pure foregut application) is low, only 16–40 %. SG achieves remission of diabetes in 50–88.8 % of patients [53, 55, 62–64]. This is comparable to DJB-SG (63 %) and II-SG (77.8 %). The value of adding complex elements to a good operation (SG) is unclear and appears unfounded. The lack of extra benefit from the foregut and hindgut elements of DJB-SG and II-SG makes the real value of foregut and hindgut theory questionable.

Authors of these papers frequently talk about the hidden element of diabetes remission and assumed it is based on the duodenum or the ileum. Whilst we agree that there is a hidden undiscovered element, it is likely to be in the stomach and further research should be focused on this organ.

Compliance with ethical standards

Disclosures Yan Mei Goh, Zaher Toumi and Ravindra S. Date have no conflicts of interest or financial ties to disclose.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent Informed consent was not required as no participants were used in this study.

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