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Meta-Analysis

Effects of Roux-en-Y Gastric Bypass and Sleeve Gastrectomy on β-Cell Function at 1 Year After Surgery: A Systematic Review

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Abstract

Bariatric surgery is a highly effective obesity treatment resulting in substantial weight loss and improved glucose metabolism. We hereby aimed to summarize available evidence of the effect of the 2 most common bariatric surgery procedures, Roux-en-Y gastric bypass (RYGB) and sleeve gastrectomy (SG), on dynamic measures of β-cell function (BCF). A systematic search of the literature was conducted in 3 bibliographic databases for studies reporting effects of RYGB and/or SG on BCF assessed using dynamic metabolic perturbation (oral or intravenous bolus stimulation), performed before and 1 year (±3 months) after surgery. Twenty-seven unique studies (6 randomized controlled trials and 21 observational studies), involving a total of 1856 obese adults, were included for final analysis. Twenty-five and 9 studies report effects of RYGB and SG on BCF, respectively (7 studies compared the 2 procedures). Seven studies report results according to presurgical diabetes status. Owing to variable testing procedures and BCF indices reported, no meta-analysis was feasible, and data were summarized qualitatively. For both surgical procedures, most studies suggest an increase in BCF and disposition index, particularly when using oral stimulation, with a more pronounced increase in diabetic than nondiabetic individuals. Additionally, limited indications for greater effects after RYGB versus SG were found. The quality of the included studies was, in general, satisfactory. The considerable heterogeneity of test protocols and outcome measures underscore the need for a harmonization of BCF testing in future research.

Key Words: β-cell function, disposition index, obesity, bariatric surgery, sleeve gastrectomy, Roux-en-Y gastric bypass

Abbreviation: AUC, area under the concentration curve; BCF, β-cell function; $\beta\text{-GS}_E$, β-cell glucose sensitivity; DI, disposition index; GLP-1, glucagon-like peptide 1; IV, intravenous; IVGTT, intravenous glucose tolerance test, MMTT, mixed meal tolerance test; NOS, Newcastle-Ottawa Quality Assessment Scale; OGTT, oral glucose tolerance test; RCT, randomized clinical trials; RoB2, Cochrane Collaboration's Tool Risk of Bias 2.

Bariatric surgery is currently the most effective therapy for sustained weight loss and improvement of obesity-related comorbidities (1). Roux-en-Y gastric bypass (RYGB) and sleeve gastrectomy (SG) are the most commonly used procedures worldwide (2). Beyond weight loss, bariatric surgery exerts powerful effects on glucose metabolism. Underlying mechanisms involve a plethora of metabolic and endocrine changes induced by the altered gastrointestinal anatomy and nutrient flow (3). Whereas 2 randomized clinical trials contrasting RYGB with SG with a 5-year follow-up period suggested comparable or only slightly larger weight loss after RYGB (below the prespecified threshold for clinical significance) (4, 5), 2 recently published meta-analyses suggest a more favorable short-term effect of RYGB over SG on achieving remission of type 2 diabetes (6, 7).

While the weight loss-induced decrease of insulin resistance substantially explains improved glucose metabolism after bariatric surgery, the altered nutrient absorption kinetics accompanied by exaggerated meal-related release of several gut hormones was proposed to directly increase β-cell function (BCF) (8). In line with this hypothesis is the late metabolic complication of bariatric surgery known as postbariatric hypoglycemia, which is characterized by an inappropriately high meal-induced insulin exposure. The condition appears to be more prevalent in RYGB than SG patients (9, 10), suggesting that the 2 procedures may differ in terms of their impact on BCF.

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To date, several studies have assessed the effect of bariatric surgery on BCF with conflicting results. In addition, studies have used varying methodologies to assess BCF and differ by time of postsurgery follow-up. Consequently, a synthesis of the results is critical to unravel possible bariatric surgery-induced changes in BCF, including potential procedure-specific effects.

Various methods exist to quantify BCF and include assessment during fasting steady-state conditions (11) or under metabolic perturbation (eg, nutrient load or pharmacological stimulation). The latter are also referred to as dynamic test protocols such as the oral glucose tolerance test (OGTT), mixed meal tolerance test (MMTT), and intravenous glucose tolerance test (IVGTT). Tests using an oral stimulus reflect overall BCF, including intrinsic cell characteristics and gut-derived insulinotropic stimulation. Ideally, assessments of BCF are based on measurements of insulin secretion derived from a modeling analysis of C-peptide since insulin undergoes substantial first-pass hepatic extraction (12). Additionally, absolute values of insulin secretion are not representative of BCF, unless glucose levels are standardized or accounted for, either empirically or using mathematical models. To provide a meaningful evaluation of BCF, it is necessary to interpret all observations within the context of insulin resistance.

The aim of this systematic review is to summarize available evidence of the effects of RYGB and SG on BCF 1 year following surgery. Furthermore, we aim to appraise the literature regarding procedure-specific effects and the role of presurgery glycemic status on the change in BCF.

Material and Methods

Data Sources and Search Strategy

This systematic review was conducted following recently published guidelines (13). Methods and results are reported in accordance with the PRISMA-S statement (14). The study protocol was registered prospectively on PROSPERO (CRD42021259003). An information specialist (B.M.) searched the following electronic databases: PubMed, Embase.com, and the Cochrane Central Register of Controlled Trials (CENTRAL), from inception to January 8, 2022. In addition, Google Scholar was searched to add possibly relevant articles where the search terms only appear in the full text. ClinicalTrials.gov was searched to identify ongoing trials. Cited references and citing references of included articles were identified via Scopus and manually screened to identify additional studies. No language or study design restriction were applied. The search strategies for the databases are summarized in Supplementary Appendix 1 (15).

Titles and abstracts were independently evaluated by 2 persons (A.B. and C.J.) according to the selection criteria. For each potentially eligible study, 1 of the 2 persons assessed the full text, which was then reviewed by a third person (D.H.). In cases of disagreement, a decision was made by consensus (A.B., C.J., D.H., and L.B.).

Study Selection and Eligibility Criteria

Studies were included if they met all of the following criteria: (1) published or registered in English language up to January 8, 2022; (2) randomized clinical trials (RCTs) or prospective observational studies including case-cohort studies, nested-case control, and prospective cohort studies; (3) included adults (age ≥ 18 years) with obesity grade ≥ II (BMI ≥ 35 kg/m^2) undergoing RYGB or SG; (4) dynamic assessment of BCF [ie, assessment of BCF following the oral ingestion of glucose (OGTT) or a mixed-meal (MMTT) or administration of intravenous glucose (IVGTT) performed before and 9 to 15 months after surgery]. Exclusion criteria were pregnancy or cancer status in the studied population and other type of research paper (case reports, abstracts, guidelines, or literature reviews).

BCF Tests

We included studies using dynamic metabolic perturbation tests, where insulin secretion was prompted by means of bolus oral (glucose or mixed meal) or intravenous (IV; glucose) stimulants. Contrasting oral with IV stimulation tests allows for unraveling the involvement of the enteroinsulinar axis in potential changes of BCF. Hyperglycemic clamp experiments, graded glucose infusion experiments, and pharmacological stimulation tests (eg, infusion of insulinotropic peptides or arginine) were excluded as they represent specific components of either the enteroinsulinar axis (eg, sensitivity of β cells to insulinotropic peptides or glucose) rather than reflecting net BCF under physiological conditions (16). Additionally, hyperglycemic clamp method or glucose-potentiated arginine stimulation tests are subject to considerable implementation heterogeneity regarding the definition of the target glycaemia (eg, different fixed levels or increment above fasting the individual's fasting glucose). Furthermore, hyperglycemic clamps provide a continuous stimulation whereas OGTT, MMTT, and IVGTTs represent bolus stimulants.

Indices of BCF

The primary focus of this review was dynamic BCF, which reflects capacity of the pancreatic β-cell to secrete insulin in response to a stimulus. The definition of BCF used in the present work encompasses the concept of β-cell sensitivity to glucose (ie, the secretion of insulin by pancreatic β-cells in response to prevailing glucose levels).

Model-based approaches derive BCF indices from a mathematical description of the relationship between glucose concentration and insulin secretion, thereby obviating the need for standardized test conditions (eg, clamping glucose to a predefined level) (17-19). In addition, various BCF indices, based on empirical formulas aiming to normalize insulin or C-peptide levels or insulin secretion (calculated using C-peptide deconvolution) with prevailing glucose levels, have been proposed (20-22). Measures of insulin alone (or C-peptide) without consideration of prevailing glucose levels were not considered.

Additionally, we extracted indices reflecting the disposition index (DI), which is a widely used insulin sensitivity-adjusted measure of BCF (23). The underlying relationship embodied in DI relates BCF and insulin sensitivity via a hyperbolic law (ie, the DI is calculated as BCF * insulin sensitivity).

Data Extraction and Analysis

Data were extracted independently by 2 reviewers (A.B. and C.J.) using a predesigned form (13), including first author and year of publication, study design, sample size, study population characteristics (sex, age, anthropometrics, diabetes status), and performed assessment of BCF (test used and reported BCF indices). In case of missing of relevant results, authors were contacted via email. Studies including either RYGB or SG with a different comparator were included as single-arm studies, and only data of the group undergoing the procedure of interest was extracted. In the event

of multiple follow-up time points, the time point closest to 1 year was chosen.

Data reported exclusively in figures were extracted using the online version of WebPlotDigitizer (24). Results reported separately for different subgroups were pooled and calculated as weighted means (by sample size) and SD across groups as described in the Cochrane Handbook (25). All data were transformed into mean and SD if not given as such in the studies (25). Because of the great diversity of used indices, with differing units, data were normalized as following to allow comparisons:

$$mean_{normalized} = \frac{mean}{SD_{pooled}},$$

$$SD_{normalized} = \frac{SD_{pooled}}{SD_{pooled}} = 1,$$

$$95\%\ CI = \frac{SD_{normalized}}{\sqrt{n_{RYGB} + n_{SG}}} \times 1.96$$

All calculations are reported in Supplementary Appendix 2 (15). Results were plotted using GraphPad Prism 8 for Windows 64-bit (Version 8.0.1, 2017, GraphPad Software, Inc.).

Study Quality Assessment

The study quality assessment was done by 2 reviewers based on the Cochrane Collaboration's Tool Risk of Bias 2 (RoB2) (26) for RCTs and a modified version of Newcastle-Ottawa Quality Assessment Scale (NOS) (27) for observational studies. RoB2 assesses 5 possible sources of bias, while NOS uses a star system to evaluate 3 domains. Nonapplicable items were removed, and the total score was adapted individually for each study [see Supplementary Appendix 3 (15)]. RCTs of which only 1 arm qualified for this work were considered as observational studies and analyzed using the NOS [this applied to Dantas et al (28) and Pournaras et al (29)].

Results

Selection Process

The selection process is summarized using the PRISMA flow chart (Fig. 1). After eliminating duplicate records, we identified a total of 5803 potentially relevant citations. After screening for titles and abstracts, 259 full-text articles were assessed for eligibility according to the predefined criteria. Twenty-eight articles, based on 27 unique studies, were included in the final analysis [2 articles (30, 31) are from the same study (Oseberg RCT) but report results from separate tests (OGTT or IVGTT)].

Study Characteristics

Among the included studies, 4 were RCTs contrasting the effects of RYGB vs SG, and 23 were observational studies (among those 20 were single-arm studies). Further study characteristics are reported in Table 1. The results encompass a total of 1856 patients. Six studies were conducted in the United States, 18 in Europe, and 3 in other countries. Fourteen studies included only patients with diabetes presurgery, while 10 studies involved mixed populations consisting of individuals with and without diabetes. Two studies included only patients without diabetes, and 1 study did not report on the diabetes status of participants. More details can be found in the Supplementary Appendix [Data Extraction File (15)].

BCF Evaluation

All studies evaluated BCF before and 12 months after surgery, except for 1 study, which performed the postsurgery BCF evaluation after 9 months (28). BCF was evaluated using oral tests in 26 studies and IV tests in 6 (5 studies report data from both oral and IV tests). Various indices of BCF are reported in the included studies. There were 10 studies estimating BCF indices using mathematical modeling: 1 study used the oral minimal model method (18), 4 studies used the IV minimal model (17), and 5 studies used the model described by A. Mari (19). In 21 studies, BCF indices derived from empirical calculations are reported (4 studies report indices both from mathematical modeling analysis and empirical calculations). An extensive overview of all indices reported in the included studies and the methods from which they were derived is provided in Tables 2 and 3.

Effect of RYGB on BCF

Twenty-five studies (9, 28-54) report effects of RYGB on BCF, encompassing a total of 1615 patients. Overall, 36 BCF indices, from 21 different studies, increased following surgery (the increase was statistically significant for 25 indices), whereas 10 decreased, with 6 indices reaching statistical significance (Fig. 2).

A fairly consistent increase following RYGB was observed in 8 out of 11 model-based indices (9, 34, 35, 39, 41, 43, 50). In the sole index showing a significant decrease [β-cell glucose sensitivity (β-GS_E)], the decrease was only apparent in participants without diabetes before surgery. In contrast, the same study reports an increase in β-GS_E in participants with type 2 diabetes mellitus (43), suggesting opposing effects depending on presurgery diabetes status (see following discussion on the influence of presurgery diabetes status). Similarly, the overall tendency of the empirical indices suggests an increase of BCF with RYGB. An increase in the insulinogenic index was reported in 8 studies (32, 33, 36, 40, 41, 45, 46, 51). However, the largest study included in the present review, with a sample size of 758 participants (of whom only 18.1% had diabetes presurgery), quantifying BCF by the insulinogenic index, did not observe any significant effect of RYGB (52). Indices calculated as the ratio of insulin and glucose exposure [using the area under the concentration curve (AUC)] showed diverging results. One study using the Stumvoll index of first-phase insulin secretion to quantify BCF (39) reported a significant decrease [a decrease, albeit not statistically significant, of the same index was also observed following SG in 2 other studies (37, 38)].

Among the studies performing IV testing, the acute insulin response (AIRg) increased in 3 studies (30, 46, 48) and decreased in 1 study (49), with differing results depending on diabetes status. Similarly, 3 out of 4 studies using indices from empirical calculations from IV tests report an increase (reaching statistical significance in 2 of them). In the study by Schrumpf et al (54), AUCins/glu decreased but AUCcp/glu increased (both significantly).

Effect of SG on BCF

Nine studies (9, 30-38) reported data on the effect of SG on BCF encompassing a total of 288 patients. Overall, 13 out of 19 BCF indices (from 8 different studies) increased postsurgery with predominantly significant results if formally tested (Fig. 3).

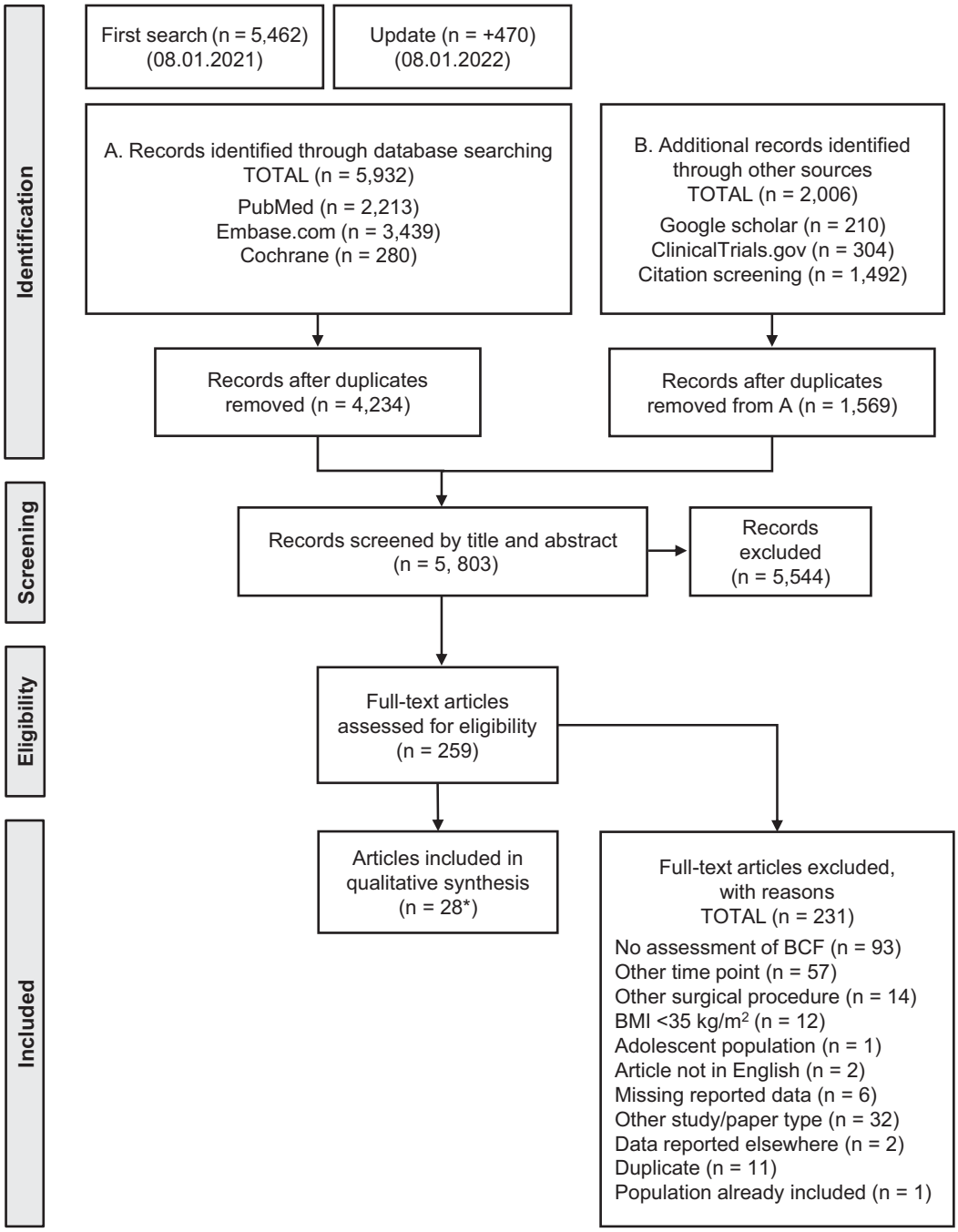

Figure 1. PRISMA flowchart showing the process for the inclusion of studies. Twenty-eight articles referring to 27 studies [2 articles (30, 31) both report results from the Oseberg-study]. Abbreviations: BCF, β-cell function; BMI, body mass index.

Five out of 6 oral model-based BCF indices reported in 3 studies increased after SG (9, 34, 35). Empirical indices showed diverging results. While there was an increase in 4 studies reporting the insulinogenic index and β-GS_E (31-33, 36, 37), results from 2 studies assessing BCF by the Stumvoll indices suggested a decrease in BCF (37, 38). Of note, studies using the Stumvoll indices also reported decreased BCF following RYGB. These contrasting findings, compared to studies using other BCF indices, may be due to the differing relationships between glucose and insulin in the calculations of BCF indices used (the Stumvoll indices are calculated using a linear combination of insulin and glucose while many other BCF calculations are based on their ratios) (Table 2). It is worth mentioning, that these formula were originally developed using data from healthy individuals (22) and may not accurately reflect BCF in a population with markedly different postprandial glucose and insulin patterns. A further study, including only nondiabetic patients (9), reported conflicting results with a decrease in the ratio of the AUC of C-peptide and glucose from 0 to 180 minutes ($AUCcp/glu_{0\text{-}180}$) and an increase when the same outcome was calculated considering only concentration above basal levels ($iAUCcp/glu_{0\text{-}180}$). In another study including 12 patients with type 2 diabetes presurgery (36), an increase in $AUCcp/glu_{0\text{-}180}$ was reported. A study including only 10 nondiabetic patients (37) reported a decrease in the ratio of the AUC for insulin over glucose calculated over 120 minutes ($AUCins/glu_{0\text{-}120}$).

Table 1. Overview of study characteristics

First author, Year	Reference	BCF evaluation	Modeling	Indices, n	BCF indices/DI	Follow-up time (months)	Sample size, n	Age, years	Sex, % female	BMI presurgery, kg/m^2	BMI at follow-up, kg/m^2	Diabetes, % baseline population
Randomized controlled trials												
RYGB vs SG												
Capristo, 2018	(9)	OGTT	Oral minimal model empirical	6	Φ_S, Φ_D, Φ, AUC cp/glu$_{0\text{-}180}$ AUC cp/glu$_{0\text{-}180\ (abl)}$ DI$_{\Phi \times Si}$	12	RYGB 25, SG 25	NA	NA	NA	NA	0.0
Fatima, 2022	(31)	OGTT	Empirical	1	β-GS$_E$	12	RYGB 53, SG 53	48.0 ± 10.0	67.0	42.0 ± 5.0	NA	100.0
Hofso, 2019	(30)	Insulin-modified IVGTT	Minimal model	2	AIR, DI$_{AIR \times Si}$		RYGB 54 (45)/41[a] SG 55 (44)/43[a]					100.0
Keidar, 2013	(32)	OGTT	Empirical	1	IGI	12	RYGB 19 (16), SG 18 (15)*	49.6 ± 10.2	45.9	42.2 ± 5.1	30.9 ± 4.0	100.0
Nemati, 2018	(33)	OGTT	Empirical	1	IGI	12	RYGB 32, SG 61	47.0 ± 3.6	50.8	40.0 ± 6.9	23.0 ± 6.2	100.0
Observational Studies												
Franzini, 2018	(34)	MMT	Mari A model	1	β-GS$_M$	12	RYGB 21, SG 8	51.9 ± 9.7	75.9	43.5 ± 5.6	30.1 ± 5.2	100.0
Nannipieri, 2013	(35)	MMT	Mari A model	2	β-GS$_M$, k$_d$	12	RYGB 23, SG 12	53.1 ± 8.5	68.6	43.4 ± 5.6	31.3 ± 4.3	100.0
Nosso, 2016	(36)	OGTT	Empirical	2	AUC ins/glu$_{0\text{-}30}$, AUC cp/glu$_{0\text{-}180}$	12	RYGB 14, SG 33	46.0 ± 9.0	57.6	44.0 ± 26.0	30.3 ± 4.1	100.0
SG												
Papamargaritis, 2013	(37)	OGTT	Empirical	6	IGI, AUC ins/glu$_{0\text{-}120}$, 1st PH, DI$_{IGI \times Ismat}$, DI$_{AUC120 \times Ismat}$, DI$_{1st\ PH \times Ismat}$	12	10	39.7 ± 9.0	70.0	47.9 ± 6.6	31.3 ± 8.2	0.0
Zetu, 2018	(38)	OGTT	Empirical	2	1st PH, 2nd PH	12	68 (60)*	41.7 ± 12.5	83.3	44.7 ± 11.2	31.0 ± 7.9	36.7
RYGB												
Antonioli, 2020	(39)	OGTT	Mari A model	1	β-GS$_M$	12	61	45.7 ± 8.6	77.0	45.3 ± 6.9	32.3 ± 2.2	47.5
Astiarraga, 2020	(40)	MMT	Empirical	1	IGI	12	12	53.0 ± 7.0	69.2	39.3 ± 1.4	25.8 ± 2.1	100.0
Bojsen-Moller, 2014	(41)	OGTT	Empirical	2	IGI$_{cp}$, DI$_{IGI \times ISclamp}$	12	20 (18)*	41.9 ± 10.2	65 (61.1)*	43.7 ± 4.5	29.6 ± 5.0	50.0
Bose, 2010	(42)	OGTT	Empirical	1	AUC ins/glu$_{0\text{-}30}$	12	11	43.0 ± 10.7	100.0	43.0 ± 5.1	30.5 ± 4.4	100.0
Camastra, 2013	(43)	MMT	Mari A Model	2	β-GS$_M$, k$_d$	12	27 (21)*	NA	NA	52.2 ± 7.3	35.0 ± 5.6	44.4 (52.4)
Dantas, 2020	(28)	OGTT	Empirical	1	DI$_{IGI \times Ismat}$	9	31	42.0 ± 7.0	100.0	47.3 ± 8.5	31.8 ± 5.4	61.3
Dutia, 2014	(44)	OGTT	Empirical	3	β-GS$_E$, AUC isr/glu$_{0\text{-}180}$, DI$_{β\text{-}GS \times 1/HOMA\text{-}IR}$	12	16 (15)*	47.1 ± 8.5	NA	43.9 ± 4.9	30.3 ± 3.7	100.0
		Iso-IVGC (Glucose matched to OGTT plasma glucose)		3	β-GS$_E$, AUC isr/glu$_{0\text{-}180}$, DI β-GS × 1/HOMA-IR							

Table 1. Continued

First author, Year	Reference	BCF evaluation	Modeling	Indices, n	BCF indices/DI	Follow-up time (months)	Sample size, n	Age, years	Sex, % female	BMI presurgery, kg/m^2	BMI at follow-up, kg/m^2	Diabetes, % baseline population
Hofso, 2011	(45)	OGTT	Empirical	4	IGI, AUC ins/glu$_{0\text{-}120}$, 1st PH, DI$_{1st\ PH \times HOMA\text{-}S}$	12	64	53.3 ± 9.2	70.3	47.3 ± 5.7	33.1 ± 5.3	46.9[b]
Holter, 2017	(46)	OGTT	Empirical	4	β-GS$_E$, IGI, DI$_{IGI \times Ismat}$, DI$_{IGI \times 1/HOMA\text{-}IR}$	12	27	43.7 ± 8.2	NA	44.6 ± 3.7	31.2 ± 3.4	100.0
		Insulin-modified IVGTT	Bergman minimal model	3	AIR, β-GS$_E$, DI$_{AIR \times Si}$							
Jorgensen, 2012	(47)	MMT	Empirical	2	β-GS$_E$, DI$_{β\text{-}GS \times 1/HOMA\text{-}IR}$	12	25 (24)*	47.7 ± 11.3	60.0	42.3 ± 5.1	32.6 ± 6.7	52.0
Khoo, 2014	(48)	insulin-modified IVGTT	Minimal model	2	AIR, DI$_{AIR \times Si}$	12	30	49.6 ± 7.7	66.7	43.4 ± 4.4	NA	100.0
Morinigo, 2006	(49)	MMT	Empirical	1	AUC ins/glu$_{0\text{-}30}$	12	34	46.3 ± 11.1	67.6	49.1 ± 5.8	33.2 ± 4.1	29.4 (35.3[c])
		IVGTT	Minimal model	2	AIR, DI$_{AIR \times 1/HOMA\text{-}IR}$							
Nannipieri, 2011	(50)	OGTT	Mari A model	2	β-GS$_M$, k$_d$	12	43	48.7 ± 8.1	67.4	45.6 ± 6.1	31.5 ± 5.6	74.4
Pournaras, 2016	(29)	MMT	Empirical	1	AUC ins/glu$_{0\text{-}180}$	12	15	47.0 ± 9.0	53.3	40.4 ± 4.4	30.4 ± 5.2	100.0
Prasad, 2022	(51)	OGTT	Empirical	4	β-GS$_E$, IGI, AUC ins/glu$_{0\text{-}180}$ DI$_{β\text{-}GS \times 1/HOMA\text{-}IR}$	12	36 (24)*	42.9 ± 8.3	79.0	42.4 ± 4.4	31.2 ± 4.8	100.0
Raverdy, 2016	(52)	OGTT	Empirical	1	IGI	12	957 (758)*	43.0 ± 11.9	74.3 (73.5)*	46.3 ± 7.7	32.4 ± 5.9	37.1 (18.3)*
Samat, 2013	(53)	MMT	Empirical	2	AUC ins/glu$_{0\text{-}30}$, AUC ins/glu$_{0\text{-}120}$, DI$_{AUC30 \times Ismat}$, DI$_{AUC120 \times Ismat}$	12	9	42.0 ± 18.0	55.6	46.0 ± 5.4	32.6 ± 3.6	100.0
Schrumpf, 1985	(54)	OGTT	Empirical	2	AUC ins/glu$_{0\text{-}180}$, AUC cp/glu$_{0\text{-}180}$	12	9	37.0 ± 10.0	55.6	NA	NA	NA
		IVGTT		2	AUC ins/glu$_{0\text{-}180}$, AUC cp/glu$_{0\text{-}180}$							

Data are expressed as mean ± SD. RCTs comparing RYGB or SG with a different comparator were included as single-arm studies and considered as observational studies for the present work.
*number of patient included in the study (number of patient at the time point post-operation, i.e. 9 to 15 months);
[a]patients included for the calculation of disposition index;
[b]abnormal glucose tolerance (defined as fasting glucose ≥ 6.1mmol/l and/or 2h-glucose ≥ 7.8mol/l;
[c]group including subjects with impaired fasting glucose, impaired glucose tolerance and new onset diabetes mellitus).
Abbreviations: BW, Body Weight; G, Glucose; I, Insulin; IVGTT, Intravenous Glucose Tolerance Test (glucose bolus infused during the test over 1 minute expressed in grams per kilograms body weight); MMT, Mixed Meal Test (consistency, total kilocalories of the meal; macronutrient composition (P - Protein, CH - Carbohydrates, F - Fat; expressed in percentage of total calories); NA, Not Available; OGTT, Oral Glucose Tolerance Test (glucose load expressed in grams of glucose); OS, Observational Study; RCT, Randomized Control Trial; T2DM, Type 2 Diabetes Mellitus; ND, Non Diabetic; TWL, Total Weight Loss

Table 2. Overview of β-cell function indices reported in the included studies

Parameter	Abbreviation	Other nomenclature found	Units	Calculation	References	Reported in following studies
Oral procedures (OGTT/MMT)						
Model-based						
Oral minimal model						
Static β-cell sensitivity	Φ_S	Static beta-cell glucose responsivity	$10^{-9}min^{-1}$	Over basal average static-phase secretion per unit over basal average glucose concentration	(55)	(9)
Dynamic β-cell sensitivity	Φ_D	Dynamic beta-cell glucose responsivity	10^{-9}	Amount of dynamic-phase secretion per unit increase of glucose concentration		(9)
Global β-cell glucose sensitivity	Φ	Total beta-cell glucose responsivity	$10^{-9}min^{-1}$	Overall (overbasal) responsivity from Φ_S and Φ_D $\Phi = \Phi_S + \frac{\Phi_D \cdot (G_{max} - G_b)}{\int_0^\infty [G(t) - b]dt}$		(9)
Mari A model						
β-cell glucose sensitivity	$\beta\text{-}GS_M$	Beta-cell glucose sensitivity	pmol × min^{-1} × m^{-2} × mmol/L	Mean slope of the dose-response function f(G) (ie, relationship between insulin secretion rates and plasma glucose concentrations during corresponding times of the test)	(19)	(34, 35, 39, 43, 50)
Rate sensitivity	k_d	Dynamic control (pd)	pmol × m^{-2} × mmol/L nmol/m^2[a]	Insulin secretory response to the positive rate of change in plasma glucose concentrations		(35, 43, 50)
Empirical						
β-cell glucose sensitivity	$\beta\text{-}GS_E$	β-cell responsiveness to glucose, O-BCGS	pmol/kg/min/(mmol/L)	Slope between insulin secretion rate and corresponding blood glucose from baseline to peak glucose level	(56)	(31, 44, 46, 47, 51)
Insulinogenic index						
IGI with insulin	IGI	$Ins_{(30\text{-}0)}/Glc_{(30\text{-}0)}$	pmol/mmol[b] μIU × dL × mL^{-1} × mg^{-1}[c]	Δinsulin 0-30/Δglucose 0-30	(57, 58)	(32, 33, 37, 40, 45, 46, 51, 52)[d]
IGI with C-peptide	IGI_{cp}		pmol/L/mM	ΔC-peptide 0-30/Δglucose 0-30		(41)
AUC parameters						
AUC insulin/AUC glucose 0-30	AUC $ins/glu_{0\text{-}30}$	First-phase glucose-stimulated insulin release[e] IGI[f]	mU/mmol[g] nmol/L/mg/dL[h,i]	AUC insulin/AUC glucose 0-30 (AUC 0-30 -IRI/AUC 0-30—glucose)[g]		(36, 42, 49, 53)
AUC insulin/AUC glucose total	AUC $ins/glu_{0\text{-}120}$	Total glucose-stimulated insulin release[j]	pmol/mmol	AUC insulin/AUC glucose $_{Tot}$ 0-120		(37, 45, 53)
AUC $ins/glu_{0\text{-}180}$		AUC insulin glucose ratio[k] Total insulinogenic index (tIGI)	Not reported	AUC insulin/AUC glucose $_{Tot}$ 0-180		(29, 51, 54)
Insulin secretion index total	AUC $isr/glu_{0\text{-}180}$	AUC insulin secretion rate/AUC glucose	pmol kg^{-1} $mmol^{-1}$	AUC-isr/AUC glucose 0–180		(44)
AUC C-peptide/AUC glucose total	AUC $cp/glu_{0\text{-}180}$	IGI 180*	nmol/pmol nmol/L/mg/dL[l,m]	AUC C-peptide/AUC glucose 0-180		(9, 36, 54)
AUC $cp/glu_{0\text{-}180\ (abl)}$			nmol/pmol	AUC C-peptide/AUC glucose 0-180 (above basal levels)		(9)

Table 2. Continued

Parameter	Abbreviation	Other nomenclature found	Units	Calculation	References	Reported in following studies
Stumvoll						
First-phase insulin release	1st PH	Estimated first phase (first-phase estimate)	pmol/L[n]	$1{,}283 + 1.829 \times \text{insulin}_{30} - 138.7 \times \text{glucose}_{30} + 3.772 \times \text{insulin}_{0}$	(22)	(37, 38, 45)
Second-phase insulin release	2nd PH	Estimated second phase (sampling times 0 and 30 minutes)	pmol/L	$286 + 0.416 \times \text{insulin 30} - 25.94 \times \text{glucose 30} + 0.926 \times \text{insulin 0}$		(38)[o]
IV procedures (IVGTT)						
Empirical						
AIRg		AUC overbasal insulin 0-10 min	(mU/L)*min[p]		(59)	
β-cell glucose sensitivity		$\beta\text{-GS}_E$	pmol/kg/min/mmol/L^{-1}	Slope between ISR and corresponding blood glucose, from baseline to peak glucose level from iso-IVGC		(30, 46, 48, 49)
AUC parameters						
AUC insulin/AUC glucose total	AUC $\text{ins/glu}_{0\text{-}90}$			AUC insulin/AUC glucose 0-90		(52)
AUC C-peptide/ AUC glucose total	AUC $\text{cp/glu}_{0\text{-}90}$			AUC C-peptide/AUC glucose 0-90		(54)
Insulin secretion index total	AUC $\text{isr/glu}_{0\text{-}180}$	ISX = AUC insulin secretion rate/ AUC glucose		AUC isr/AUC glucose 0-180		(44)

[a]In Nannipieri et al (50) and Camastra et al (43).
[b]Not reported in Nemati et al (33), Papamargaritis et al (37), or Raverdy et al (52).
[c]In Astiarraga et al (40).
[d]Calculation and time point are not specified in Nemati et al (33).
[e]In Samat et al (53).
[f]AUC insulin over AUC glucose was reported as IGI in Bose et al (42).
[g]In Morinigo et al (49).
[h]In Nosso et al (36).
[i]Unit not reported in Bose et al (42) and Samat et al (53).
[j]In Samat et al (53).
[k]In Pournaras et al (29).
[l]Insulin secretion rate.
[m]In Nosso et al (36).
[n]Units are not reported in Schrumpf et al (54).
[o]Units are not reported in Papamargaritis et al (37).
[p]Insulin was measured only at 0 and 30 minutes in Zetu et al (38).
Abbreviations: AUC, area under the concentration curve; IGI, insulinogenic index; IRI, insulin radioimmunoassay; ISR, insulin secretion rate; IVGTT, intravenous glucose tolerance test; MMT, mixed meal tolerance test; OGTT, oral glucose tolerance test; PH, phase; AIR, acute insulin response to intravenous glucose.

Table 3. Overview of the disposition indices reported in the included studies

Abbreviation	Other nomenclature found	Units	Calculation	References	Reported in the following studies
Oral procedures (OGTT/MMT)					
Model-based					
$DI_{\Phi \times Si}$		10^{-14} dL × kg^{-1} × min^{-2}/pmol × L^{-1}	β-cell glucose sensitivity Φ × whole body insulin sensitivity S_i	(55)	(9)
Empirical					
$DI_{\beta\text{-GS} \times 1/\text{HOMA-IR}}$		—	β-GS × 1/HOMA-IR	(60, 61)	(44, 47, 51)
$DI_{\text{IGI} \times \text{ISmat}}$	β-cell function index[a]	—	IGI (Δinsulin 0-30/Δglucose 0-30) × Matsuda index	(23, 60)	(28, 37, 46)
$DI_{\text{IGI} \times \text{ISclamp}}$		—	IGI × insulin sensitivity (Rd_{clamp}/$insulin_{clamp}$)[b]	(62)	(41)
$DI_{\text{IGI} \times 1/\text{HOMA-IR}}$		—	IGI × 1/HOMA-IR	(63)	(46)
$DI_{\text{AUC30} \times \text{ISmat}}$	β-cell function 0-30/first phase oral disposition index	—	AUC Ins 0-30/AUC Glc 0-30 × Matsuda index		(53)
$DI_{\text{AUC120} \times \text{ISmat}}$	Oral dispostion indexβ-cell function 0-120/total oral disposition index	—	AUC insulin 0-120/ AUC glucose 0-120 × Matsuda index	(23)	(37, 53)
$DI_{\text{1st PH} \times \text{ISmat}}$		—	First-phase Stumvoll index × Matsuda index	(23)	(37)
$DI_{\text{1st PH} \times \text{HOMA-S}}$		—	First-phase Stumvoll index × HOMA-S	(23)	(45)
IV procedures (IVGTT)					
Empirical					
$DI_{\text{AIR} \times \text{Si}}$		—	AIRg × whole body insulin sensitivity Si	(59)	(30, 46, 48)
$DI_{\text{AIR} \times 1/\text{HOMA-IR}}$	AIRg × 1/HOMA-IR[c]	—	AIRg × 1/HOMA-IR	(59)	(49)
$DI_{\beta\text{-GS} \times 1/\text{HOMA-IR}}$		—	β-GS × 1/HOMA-IR	(60, 61)	(44)[d]

[a]Unit reported as following in Khoo et al (48).
[b]Referred with this nomenclature in figures in Dantas et al (28).
[c]Rd measured using a hyperinsulinemic-euglycemic clamp.
[d]Not reported as disposition index.
Abbreviations: DI, disposition index; IGI, insulinogenic index; IRI, insulin radioimmunoassay; IS, insulin sensitivity; ISI, insulin sensitivity index; IVGTT, intravenous glucose tolerance test; MMT, mixed meal tolerance test; OGTT, oral glucose tolerance test; Rd, rate of disappearance.

Effect of RYGB versus SG on BCF

The effects of RYGB and SG on BCF were compared in 7 studies [4 RCTs (9, 30-33) and 3 observational studies (34-36)], including a total of 185 and 166 patients undergoing RYGB and SG, respectively (Fig. 4).

From the 3 studies (9, 34, 35) using BCF indices derived from mathematical modeling, only 1 reported a significant difference between the 2 bariatric procedures (9). This RCT, including 120 nondiabetic participants, using the oral minimal model (9) to derive BCF indices from an OGTT, demonstrated distinct changes in dynamic β-cell sensitivity (Φ_D) between procedures, with a decrease in RYGB and an increase in SG. One out of 6 studies reporting BCF indices from empirical calculations did report a significant difference between the 2 procedures in their effect on BCF. Of note, statistical comparisons between the 2 procedures were carried out in only 3 out of the 7 empirical indices. However, a larger improvement in favor of RYGB can be observed for most of the empirical indices (Fig. 4). For example, the RCT including 100 diabetic patients performed by Fatima et al in the Oseberg RCT (31) showed a greater increase in oral $\beta\text{-GS}_E$ in RYGB compared to SG. Of note, the same study [published in (30)] did not observe any difference between the procedures when BCF was assessed using IV testing.

Influence of the Presurgery Diabetes Status on the Changes in BCF

Seven studies (39, 41, 43, 45, 47, 49, 50) reported data regarding the influence of presurgery diabetes status on the change of BCF with RYGB (whereas none with SG). Overall, the results suggest a greater increase in BCF in individuals with diabetes vs those without. Five studies reported comparable increased (or marginally in favor of subjects with diabetes). In 3 studies, BCF increases in individuals with diabetes, while BCF remained unchanged in the nondiabetic group.

Two studies using oral (43) or IV (49) tests, respectively, reported an increase in BCF following RYGB in the diabetic group but a decrease in the nondiabetic group (Fig. 5).

Effect of RYGB on the DI

A consistent increase in the DI following RYGB surgery was observed in all 12 studies (11 of which reached statistical significance). The increase in the DI was evident both in studies using oral and IV tests without any clear difference in the magnitude of the change.

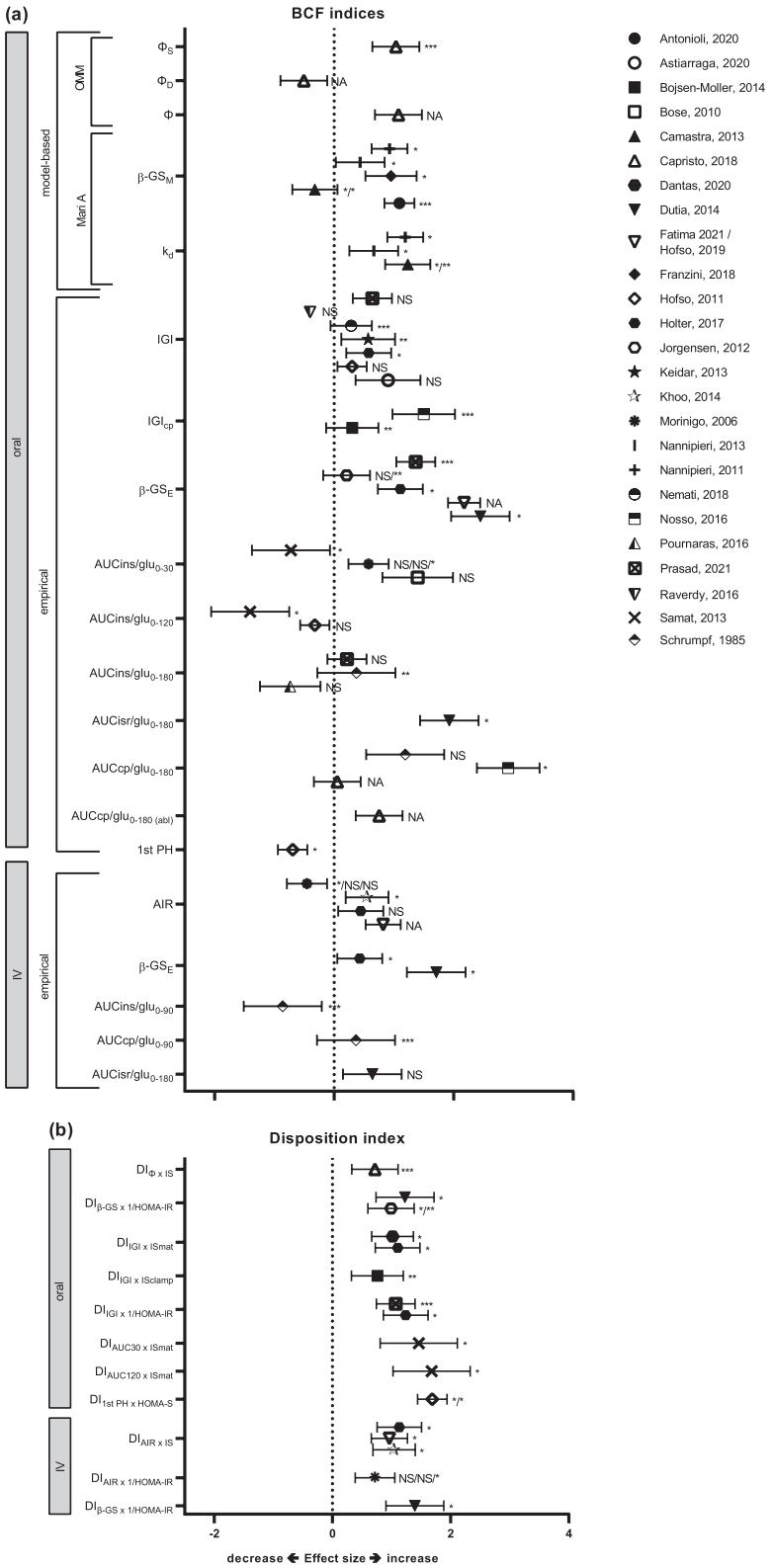

Figure 2. Effects of Roux-en-Y gastric bypass (RYGB) on β-cell function (BCF) indices (A) and the disposition index (DI) (B). Illustration of individual effects of RYGB on indices of BCF. Some studies reported >1 index; this may lead to overrepresentation of the study in the figure, and hence misinterpretation. DI calculation is denoted as a subscript (B). Outcomes are reported as effect size with plots representing normalized mean and 95% CI. Significance level reported from the studies: *reported as significant and/or $P < 0.05$; **$P < 0.01$, ***$P < 0.001$. When results were only reported separately according to presurgery diabetes status, significance level was displayed separately, separated by "/" [nondiabetic/diabetic or nondiabetic/prediabetes/diabetes as in Morinigo et al (49)]. Abbreviations for BCF indices are reported in Tables 2 and 3. Abbreviations: BCF, β-cell function; DI, disposition index; NA, nonavailable; NS, nonsignificant.

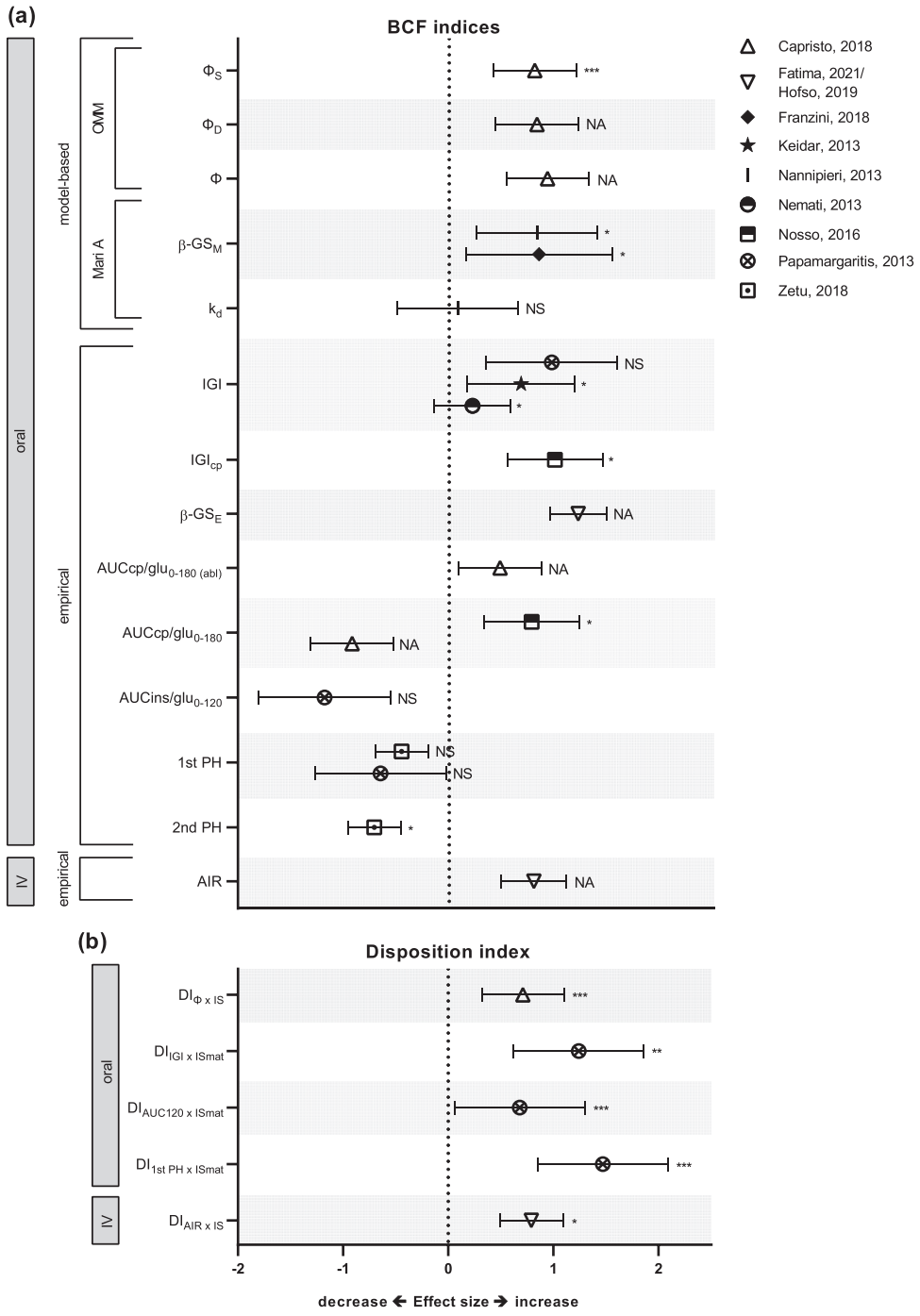

Figure 3. Effect of sleeve gastrectomy (SG) on β-cell function (BCF) indices (A) and the disposition index (DI) (B). Illustration of individual effects of SG on indices of BCF. DI calculation is denoted as a subscript (B). Some studies reported >1 index; this may lead to overrepresentation of the study in the figure, and hence misinterpretation. Outcomes are reported as effect size with plots representing normalized mean and 95% CI. Significance level reported from the studies: *reported as significant and/or $P < 0.05$; **$P < 0.01$, ***$P < 0.001$. Abbreviations for BCF indices are reported in Tables 2 and 3. Abbreviations: BCF, β-cell function; DI, disposition index; NA, nonavailable; NS, nonsignificant.

Effect of SG on the DI

A significant increase in DI after SG was reported in all indices across the 3 studies, of which 2 used oral (9, 37) and 1 IV stimulation tests (31).

Effect of RYGB vs SG on the DI

Only 2 studies compared the effect of RYGB vs SG on the DI. None of them reported any difference in the effect on the DI between the 2 procedures (9, 30).

Influence of the Presurgery Diabetic Status on the Changes in DI

As described in the previous section, DI parameters increased in all studies. All 3 studies assessing changes in the DI according to the presurgery diabetic status report greater increase in patients with type 2 diabetes before surgery compared to nondiabetic individuals. The largest difference in favor of type 2 diabetes was reported in a study by Bojsen-Møller et al (41), with a normalized effect size above 5 for the subgroup with type 2 diabetes (due to a 4-fold increase in DI

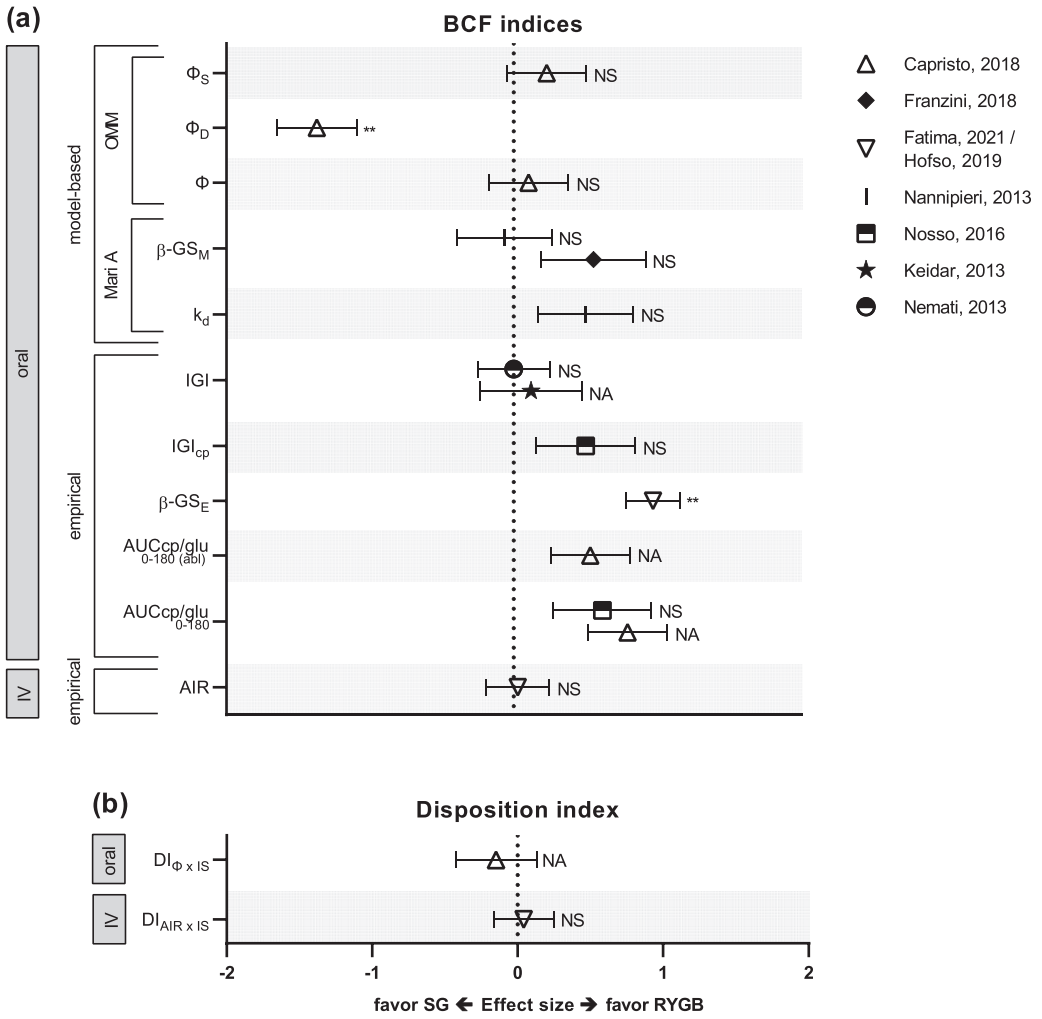

Figure 4. Effect of Roux-en-Y gastric bypass (RYGB) vs sleeve gastrectomy (SG) on β-cell function (BCF) indices (A) and the disposition index (DI) (B). Comparison of the effects of RYGB and SG on indices of BCF (A) and DI (B). Some studies reported >1 index; this may lead to overrepresentation of the study in the figure, which can lead to misinterpretation. DI calculation is denoted as a subscript (B). Outcome are reported as effect size with plots representing normalized mean and 95% CI. Significance level reported from the studies: *reported as significant and/or $P < 0.05$; ** $P < 0.01$, *** $P < 0.001$. Abbreviations for BCF indices are reported in Tables 2 and 3. Abbreviations: BCF, β-cell function; DI, disposition index; NA, nonavailable; NS, nonsignificant.

and a low reported SD), while it only increased moderately for the nondiabetic subgroup.

Study Quality

According to the RoB2 assessment, 2 of the RCTs (9, 30, 31) (the 2 articles of the Oseberg RCT were assessed together) had low risk of bias, and 2 RCTs had high risk of bias (32, 33). The most prominent cause for a poor-quality RCT was missing outcome data. According to the NOS assessment, 23 of the analyzed studies were rated good quality, of which 14 reached maximum score and 8 reached 4 out of 5 points. Only 1 study was appointed a lower score (42). Individual results of the study quality assessment of all included studies can be found in the Supplementary Appendix 4 (15).

Discussion

In this work, we summarized the available evidence from 27 studies investigating the effect of RYGB and SG on dynamic measures of BCF at 1 year (±3 months) of postsurgery follow-up. Additionally, we assessed procedure-specific effects as well as the impact of the presurgery diabetes status. Overall, available evidence supports an increased in BCF after both procedures. The majority of the reported BCF indices increase following surgery, with similar results irrespective of their calculation using mathematical models or empirical formulas. While results for changes in BCF showed a certain variability, a clear increase for both bariatric procedures was apparent for the DI, which emphasizes the importance of interpreting BCF in the context of insulin sensitivity.

When comparing the effects of RYGB and SG on BCF based on the limited available evidence (only 7 head-to-head comparisons of which 4 were RCTs with small samples sizes), there was no clear superiority of either procedure. However, the overall picture of the available studies is suggestive of a more prominent increase in BCF following RYGB (Fig. 4). The potential superiority of RYGB vs SG likely relates to the marked postsurgical anatomical differences between the procedures, which leads to distinct nutrient absorption and gut peptide secretory profiles [notably glucagon-like peptide 1 (GLP-1), glucose-dependent insulinotropic peptide,

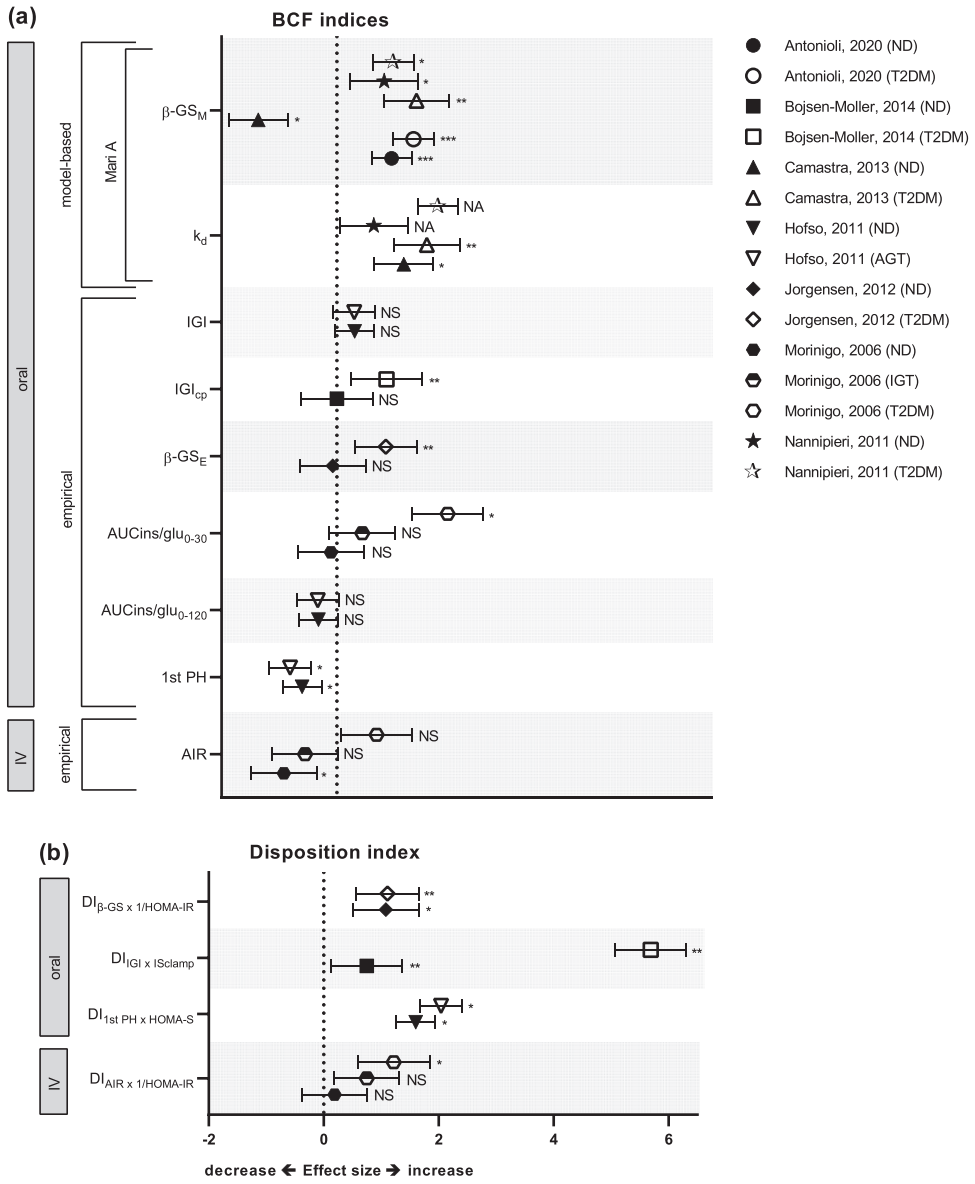

Figure 5. Effect of Roux-en-Y gastric bypass (RYGB) on β-cell function (BCF) indices (A) and the disposition index (DI) (B) according to presurgery diabetes status. Filling status of icons represents diabetes status: filled icons are indicative nondiabetic individuals, half-filled icon represent prediabetic individuals (impaired glucose tolerance), and empty icons represent subjects with type 2 diabetes. Outcome are reported as effect size with plots representing normalized mean and 95% CI. Significance level reported from the studies: *reported as significant and/or $P < 0.05$; ** $P < 0.01$, *** $P < 0.001$. DI calculation is highly heterogeneous and is reported as inferior character. Abbreviations for BCF indices are reported in Tables 2 and 3. Abbreviations: BCF, β-cell function; DI, disposition index; NA, nonavailable; NS, nonsignificant.

oxyntomodulin, and peptide tyrosine- tyrosine] (3). A larger effect of RYGB vs SG on BCF may explain the greater prevalence of postbariatric hypoglycemia observed in RYGB patients (9, 10). While the underlying of this metabolic disorder appears multifactorial, excessive stimulation of the enteroinsulinar axis in affected patients was demonstrated to be a key contributor (64, 65).

The present review included studies using dynamic bolus stimulation tests, where insulin secretion is induced by means of an oral (pure glucose or a mixed nutrients) or IV stimulus (glucose). The increase in BCF is notably apparent independently of the used administration route (oral or IV), albeit only few studies report results from IV tests. An increase in BCF in an IV test would support the hypothesis that intrinsic factors, such as an increase in β-cell mass, an alteration in the stimulus sensing, or stimulus-secretion coupling of β cells contributes to changes in BCF following bariatric surgery (66). Such intrinsic alterations may ultimately reflect trophic effects of gut factors.

Hyperglycemic clamp experiments, graded glucose infusions, and other pharmacological stimulation tests were excluded from the present work as these tests reflect specific components of either the enteroinsulinar axis or BCF and imply a nonphysiological and/or continuous stimulation of insulin secretion. However, these experiments are still considered the gold standard to assess β-cell sensitivity to glucose and, in the case of an additional infusion of GLP-1, β-cell sensitivity to GLP-1. In the only study, known to us, that examined BCF using a combined with GLP-1 infusion before and 1 year after RYGB a reduction in insulin

secretion in response to glucose as well as to GLP-1 was observed (67). Other studies that performed clamp experiments at different time points after RYGB obtained similar results (68-70). These results are in contrast to findings of IVGTT studies that observed surgery-induced increases in BCF. Discrepancies may be due to aforementioned different types of β-cell stimulation or limitations in methodologies and study designs, underscoring the need for further investigation.

The analysis of the effect of presurgery diabetes status on the changes in BCF suggests a greater improvement in patients with diabetes, although the values of BCF postsurgery remained below the physiological level of normal glucose tolerant participants (pre- and postsurgery) in most of the included studies (39, 41, 43, 45, 47, 49, 50). Of note, when considering only results from the nondiabetic groups, no clear trend toward an increase in BCF can be identified. This finding is further corroborated by the fact that in the large study by Raverdy et al (52), in which only 18% of the 758 participants had diabetes before surgery, no increase in BCF was observed. Apart from the heterogeneity of the methodologies and small sample sizes, conflicting results between studies in diabetic patients may also arise from differences in the disease status at baseline (eg, time since diagnosis, insulin requirements, etc) and the natural course of the disease.

Further differences in outcomes between studies could result from the type of oral stimulus used (OGTT or MMT). In addition to different glucose absorption kinetics and enteroendocrine responses, amino acid–induced alterations in postprandial glucagon responses between OGTT and MMT may also play a role (71). Although no apparent effect can be identified in the present work, the different insulinotropic effect of glucagon depending on the macronutrient composition of the meal stimulus could influence measured changes in BCF. To our knowledge, this is the first systematic review of the effect of bariatric surgery on BCF. To reduce the risk of publication bias, a highly sensitive search strategy was created, and additional resources were searched including ClinicalTrials.gov and Google Scholar, as well as forward and backward screening of the references. Furthermore, to reduce heterogeneity between the studies, we focused only on BCF evaluations at a strictly determined postsurgery time point and only with the use of dynamic testing. However, our work has some limitations. Sample sizes of included studies were relatively small with only 2 trials involving more than 100 participants, and only 6 of the 26 studies were RCTs. While functional measures are a crucial requirement to interrogate the effect of bariatric surgery on β cells, a major caveat is the lack of a clear definition of BCF and guideline for outcome testing in clinical trials. This resulted in various different BCF indices and a high level of heterogeneity between reported results, thereby preventing conclusive answers regarding procedure-specific effects.

Although mathematical modeling may provide benefits regarding convenience of test performance and physiological insights, model-specific output variables challenge comparability between studies, and none of the currently used models to estimate BCF have been validated for their use in a postbariatric population. However, despite the known limitations of individual models, the use of model-based approaches underscores the complexity of BCF, which cannot be reduced to a single parameter (as typically done with the empirical indices) (72). Further work on harmonizing BCF testing and validation of mathematical models in the postbariatric population is important to advance our knowledge and ensure comparability of study outcomes. As a starting point, the present work may provide a useful overview of commonly used dynamic BCF indices in clinical research.

The findings of this work suggest that bariatric surgery, both RYGB and SG, exert powerful effects on BCF. Thus, the potential for research in this area appears very promising as deeper mechanistic insights could unravel important therapeutic targets. The ongoing Oseberg RCT (ClinicalTrials.gov identifier: NCT01778738) may soon expand available evidence with additional data on procedure-specific effects on BCF. The state of current knowledge is still limited but sufficient to support the design and application of larger and adequately powered studies with harmonized outcomes of BCF and well-phenotyped populations. Carefully planned subgroup analyses are warranted to further our understanding of the influence of the presurgery diabetes status and procedure-specific effects.

In conclusion, the present work supports enhancement of dynamic measures of BCF 1 year after both RYGB and SG. Although some indications exist for more pronounced effects after RYGB vs SG and formerly diabetic vs nondiabetic individuals, substantial heterogeneity of reported BCF and low sample sizes challenge conclusive statements. Harmonization of BCF-assessment and larger trials are an essential requirement to clarify remaining uncertainties.

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Author Contributions

Conceptualization, L.B. and D.H; methodology, L.B., D.H., and T.M.; literature search, A.B., C.J., C.K., and B.M.; data extraction, A.B. and C.J.; interpretation, A.B, C.J., M.S, C.D.M, C.T.N, D.H., and L.B.; writing (original draft preparation), A.B., C.J., and D.H; writing (review and editing), T.M., M.S, C.D.M, C.T.N, D.H., and L.B.; visualization, A.B., C.J., and D.H.; supervision, D.H. and L.B. All authors have reviewed the manuscript and approved its final version.

Disclosures

The authors have nothing to disclose.

Data Availability

Access to data collected from this study will be made available following publication upon email request to the corresponding author.

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