Effects of Roux-en-Y gastric bypass and sleeve gastrectomy on β-cell function at one 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 two 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 1,856 obese adults were included for final analysis. 25 and 9 studies report effects of RYGB and SG on BCF respectively (7 studies compared the two procedures). 7 studies report results according to pre-surgical diabetic 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 non-diabetic individuals. Additionally, limited indications for greater effects after RYGB and SG was found. The quality of the included studies was in general satisfactory. The considerable heterogeneity of test protocols and outcome measures underscores 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

Introduction

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 two randomized clinical trials contrasting RYGB with SG with 5-year follow-up period suggested comparable or only slightly larger weight-loss after RYGB (4, 5) (below the pre-specified threshold for clinical significance), two recently published meta-analyses suggest a more favorable short-term effect of RYGB over SG on achieving remission of type 2 diabetes (6, 7).

Whilst 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 on 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 post-bariatric 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 two procedures may differ in terms of their impact on BCF.

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 post-surgery 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 (e.g., 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 modelling 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 one year following surgery. Furthermore, we aim to appraise the literature regarding procedure-specific effects and the role of pre-surgery 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 08.01.2022. 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 in order 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 the supplementary material (Appendix 1 (15)).
Titles and abstracts were independently evaluated by two persons (A.B., C.J.) according to the selection criteria. For each potentially eligible study, one of the two 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., L.B.).

Study selection and eligibility criteria

Studies were included if they met all of the following criteria: (i) published or registered in English language up to 08.01.2022; (ii) randomized clinical trials (RCTs) or prospective observational studies including case-cohort studies, nested-case control and prospective cohort studies (OS); (iii) included adults (age ≥ 18 years) with obesity grade ≥ II (BMI ≥ 35 kg/m^2) undergoing RYGB or SG; (iv) dynamic assessment of BCF (i.e. 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 unravelling the involvement of the entero-insulinar axis in potential changes of BCF. Hyperglycaemic clamp experiments, graded glucose infusion experiments, as well as pharmacological stimulation tests (e.g., infusion of insulinotropic peptides or arginine) were excluded as they represent specific components of either the entero-insulinar axis (e.g. sensitivity of beta-cells to insulinotropic peptides or glucose) rather than reflecting net BCF under physiological conditions (16). Additionally, hyperglycaemic clamp method or glucose-potentiated arginine stimulation tests are subject to considerable implementation heterogeneity regarding the definition of the target glycaemia (e.g. different fixed levels or increment above fasting the individual's fasting glucose). Furthermore, hyperglycaemic 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 beta-cell to secrete insulin in response to a stimulus. The definition of BCF used in the present work encompass the concept of beta-cell sensitivity to glucose (i.e. the secretion of insulin by pancreatic beta-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 standardised test conditions (e.g., clamping glucose to a predefined level) (17-19). In addition, various BCF indices, based on empirical formulas aiming to normalise 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, i.e. the DI is calculated as BCF * insulin sensitivity.

Data extraction and analysis

Data were extracted independently by two reviewers (A.B., 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 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 one 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 standard deviations (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 the supplementary material (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 two 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 five possible sources of bias, while NOS uses a star system to evaluate three domains. Non applicable items were removed and total score was adapted individually for each study (see Appendix 3 in the supplementary material (15)). RCTs of which only one arm qualified for this work were considered as observational studies and analysed using the NOS (this applied for (28) and (29)).

Results

Selection process

The selection process is summarized using the PRISMA flow chart (Figure 1). After eliminating duplicate records, we identified a total of 5,803 potentially relevant citations. After screening for titles and abstracts, 259 full-text articles were assessed for eligibility according to the predefined criteria. 28 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 characteristic

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 1,856 patients. Six studies were conducted in the USA, 18 in Europe, and 3 in other countries. Fourteen studies included only patients with diabetes pre-surgery, 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 diabetes status of participants. More details can be found in the supplementary material (Data extraction file (15)).

BCF evaluation

All studies evaluated BCF before and 12 months after surgery, except for 1 study which performed the post-surgery 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 modelling (1 study used the Oral Minimal Model (OMM) method (18), 4 studies used the IV Minimal Model (IVMM) (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 modelling analysis

and empirical calculations). An extensive overview of all indices reported in the included studies, and the methods they were derived from, is provided in Table 2 and Table 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 (increase was statistically significant for 25 indices), whereas 10 decreased, with 6 indices reaching statistical significance (Figure 2).

A fairly consistent increase following RYGB was observed in 8 out of 11 model-based indices (9, 32, 34, 36, 38, 44, 45). In the sole index showing a significant decrease (β-cell glucose sensitivity (β-GS_M)), the decrease was only apparent in participants without diabetes before surgery. In contrast, the same study reports an increase in β-GS_M participants with T2DM (36), suggesting opposing effects depending on pre-surgery diabetes status (see section below on the influence of pre-surgery diabetic 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 (33, 34, 39, 40, 46, 48, 53, 54). However, the largest study included in the present review, with a sample size of 758 participants (of whom only 18.1% had diabetes pre-surgery), quantifying BCF by the insulinogenic index, did not observe any significant effect of RYGB (49). 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), report a significant decrease (a decrease albeit not statistically significant of the same index was also observed following SG in 2 other studies (47, 52)).
Among the studies performing IV testing, the model-based acute insulin response (AIR) increased in 3 studies (30, 40, 42) and decreased in 1 study (43), 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 and colleagues (51), AUCins/glu decreases but AUCcp/glu increases (both significantly).

Effect of SG on BCF

Nine studies (9, 30, 31, 38, 44, 46, 47, 52-54) 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 post-surgery with predominantly significant results if formally tested (Figure 3).

Five out of 6 oral model-based BCF indices reported in 3 studies increased after SG (9, 38, 44). Empirical indices showed diverging results. While there was an increase in 4 studies reporting the insulinogenic index and β-GS_E (31, 46, 47, 53, 54), results from 2 studies assessing BCF by the Stumvoll indices suggest a decrease in BCF (47, 52). Of note, studies using the Stumvoll indices also reported decreasd 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 on data from healthy individuals (22) and may not accurately reflect BCF in a population with highly different postprandial glucose and insulin levels). A

further study, including only non-diabetic patients (9), report conflicting results with a decrease in the ratio of the area under the curve of C-peptide and glucose from 0 to 180 minutes ($AUCcp/glu_{0-180}$) and an increase when the same outcome was calculated considering only concentration above basal levels ($iAUCcp/glu_{0-180}$). In another study including 12 patients with type 2 diabetes pre-surgery (46), an increase in $AUCcp/glu_{0-180}$ was reported. A study including only 10 non-diabetic patients (47) report a decrease in the ratio of the area under the curve for insulin over glucose calculated over 120 min ($AUCins/glu_{0-120}$).

Effect of RYGB versus SG on BCF

The effects of RYGB and SG on BCF were compared in 7 studies (4 RCTs (9, 30, 31, 53, 54) and 3 observational studies (38, 44, 46)), including a total of 185 and 166 patients undergoing RYGB and SG, respectively (Figure 4).

From the 3 studies (9, 38, 44) using BCF indices derived from mathematical modelling, only 1 reports a significant difference between the 2 bariatric procedures (9). This RCT, including 120 nondiabetic participants, using the OMM (9) to derive BCF indices from an OGTT, reports 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 (Figure 4). For example, the RCT including 100 diabetic patients performed by Fatima and colleagues in the Oseberg RCT (31) showed a greater increase in oral β-cell glucose sensitivity ($\beta\text{-}GS_E$) 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 pre-surgery diabetic status on the changes in BCF

Seven studies (32, 34, 36, 39, 41, 43, 45) report data regarding the influence of pre-surgery 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 report comparable increases (or marginally in favor of subjects with diabetes). In 3 studies, BCF increases in individuals with diabetes, while BCF remains unchanged in the non-diabetic group.

Two studies using oral (36) or IV (43) tests, respectively, report an increase in BCF following RYGB in the diabetic group but a decrease in the non-diabetic group (Figure 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 DI was evident both in studies using oral and IV tests without any clear difference in the magnitude of the change.

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, 47) and 1 IV stimulation tests (31).

Effect of RYGB versus SG on the DI

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

Influence of the pre-surgery diabetic status on the changes in DI

As described above, DI parameters increased in all studies. All 3 studies assessing changes in the DI according to the pre-surgery diabetic status report greater increase in patients with type 2 diabetes predating surgery compared to non-diabetic individuals. The largest difference in favor of type 2 diabetes was reported in a study by Bojsen-Møller and colleagues (34), with a normalized effect size above 5 for the subgroup with type 2 diabetes (due to a fourfold increase in DI and a low reported SD), while it only increased moderately for the non-diabetic 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 (53, 54). 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 pointed a lower score (35). Individual results of the study quality assessment of all included studies can be found in the supplementary material (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 post-surgery follow-up. Additionally, we assessed procedure-specific effects as well as the impact of the pre-surgery diabetes status. Overall, available evidence supports an increase 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 show a certain variability, a clear increase for both bariatric procedures is 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 RCTs and 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 (Figure 4). The potential superiority of RYGB vs. SG likely relates to the marked post-surgical 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 (GIP), oxyntomodulin and peptide tyrosine- tyrosine (PYY)) (3). A larger effect of RYGB vs. SG on BCF may explain the greater prevalence of post-bariatric hypoglycemia observed in RYGB patients (9, 10). While the underlying pathophysiology appears multi-factorial, excessive stimulation of the entero-insulinar axis in affected patients was demonstrated to be a key contributor (55, 56).

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 beta-cell mass or an alteration in the stimulus sensing or stimulus-secretion coupling of beta-cells contribute to changes in BCF following bariatric surgery (57). Such intrinsic alterations may ultimately reflect trophic effects of gut factors.

Hyperglycemic clamp experiments, graded glucose infusions, and other pharmacological stimulation tests have been excluded from the present work as these tests reflect specific components of either the entero-insulinar axis or BCF and imply a non-physiological and/or continuous stimulation of insulin secretion. However, these experiments are still considered the gold standard to assess beta-cell sensitivity to glucose and, in the case of an additional infusion of GLP-1, beta-cell sensitivity to GLP-1. In the only study, of which we are aware, that examined BCF using a hyperglycemic clamp before and one year after bariatric surgery, Elahi and colleagues reported a reduction in insulin secretion in response to glucose as well as to GLP-1 during a hyperglycemic clamp with the concomitant infusion of GLP-1 one year after RYGB (58). Other studies that performed clamp experiments at different time points after RYGB obtained similar results (59-61). These results are in contrast to findings of IVGTT studies which observed surgery-induced increases in BCF. Discrepancies may be due to aforementioned different types of beta-cell stimulation or limitations in methodologies and study designs, underscoring the need for further investigation.

The analysis of the effect of pre-surgery diabetic status on the changes in BCF suggests a greater improvement in patients with diabetes, although the values of BCF post-surgery remained below the physiological level of normal glucose tolerant participants (pre- and post-surgery) in most of the included studies (32, 34, 36, 39, 41, 43, 45). Of note, when considering only results from the non-diabetic groups, no clear trend towards an increase in BCF can be identified. This finding is further corroborated by the fact that in the large study by Raverdy and colleagues (49), 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 (e.g. 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 (62). 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, 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 post-surgery 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 the beta-cell, 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 modelling 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 post-bariatric 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) (63). Further work on harmonizing BCF testing and validation of mathematical models in the post-bariatric 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 support 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 pre-surgery glycaemic status and procedure-specific effects.

In conclusion, the present work supports enhancement of dynamic measures of BCF one year after both RYGB and SG. Although some indications exist for more pronounced effects after RYGB vs. SG and formerly diabetic vs. non-diabetic 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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Data availability

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

Author contribution

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.

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Abbreviation: BCF, Beta-cell function. IV, intra-venous, IVGTT, intravenous glucose tolerance test. MMTT, mixed meal tolerance test. OGTT, oral glucose tolerance test. Abbreviation of beta-cell function indices are reported in Table 2 and Table 3.

References

1. Sjostrom, L., K. Narbro, C.D. Sjostrom, K. Karason, B. Larsson, H. Wedel, T. Lystig, M. Sullivan, C. Bouchard, B. Carlsson, C. Bengtsson, S. Dahlgren, A. Gummesson, P. Jacobson, J. Karlsson, A.K. Lindroos, H. Lonroth, I. Naslund, T. Olbers, K. Stenlof, J. Torgerson, G. Agren, L.M. Carlsson, and S. Swedish Obese Subjects, *Effects of bariatric surgery on mortality in Swedish obese subjects.* N Engl J Med, 2007. **357**(8): p. 741-52.
2. Angrisani, L., A. Santonicola, P. Iovino, A. Vitiello, K. Higa, J. Himpens, H. Buchwald, and N. Scopinaro, *IFSO Worldwide Survey 2016: Primary, Endoluminal, and Revisional Procedures.* Obes Surg, 2018. **28**(12): p. 3783-3794.
3. Svane, M.S., K.N. Bojsen-Moller, C. Martinussen, C. Dirksen, J.L. Madsen, S. Reitelseder, L. Holm, J.F. Rehfeld, V.B. Kristiansen, G. van Hall, J.J. Holst, and S. Madsbad, *Postprandial Nutrient Handling and Gastrointestinal Hormone Secretion After Roux-en-Y Gastric Bypass vs Sleeve Gastrectomy.* Gastroenterology, 2019. **156**(6): p. 1627-1641 e1.
4. Peterli, R., B.K. Wölnerhanssen, T. Peters, D. Vetter, D. Kröll, Y. Borbély, B. Schultes, C. Beglinger, J. Drewe, M. Schiesser, P. Nett, and M. Bueter, *Effect of Laparoscopic Sleeve Gastrectomy vs Laparoscopic Roux-en-Y Gastric Bypass on Weight Loss in Patients With Morbid Obesity: The SM-BOSS Randomized Clinical Trial.* JAMA, 2018. **319**(3): p. 255-265.
5. Salminen, P., M. Helmiö, J. Ovaska, A. Juuti, M. Leivonen, P. Peromaa-Haavisto, S. Hurme, M. Soinio, P. Nuutila, and M. Victorzon, *Effect of Laparoscopic Sleeve Gastrectomy vs Laparoscopic Roux-en-Y Gastric Bypass on Weight Loss at 5 Years Among Patients With Morbid Obesity: The SLEEVEPASS Randomized Clinical Trial.* JAMA, 2018. **319**(3): p. 241-254.
6. Castellana, M., F. Procino, E. Biacchi, R. Zupo, L. Lampignano, F. Castellana, R. Sardone, A. Palermo, R. Cesareo, P. Trimboli, and G. Giannelli, *Roux-en-Y Gastric Bypass vs Sleeve Gastrectomy for Remission of Type 2 Diabetes.* J Clin Endocrinol Metab, 2021. **106**(3): p. 922-933.
7. Borgeraas, H., D. Hofsø, J.K. Hertel, and J. Hjelmesaeth, *Comparison of the effect of Roux-en-Y gastric bypass and sleeve gastrectomy on remission of type 2 diabetes: A systematic review and meta-analysis of randomized controlled trials.* Obes Rev, 2020. **21**(6): p. e13011.
8. Chen, X., J. Zhang, and Z. Zhou, *Targeting Islets: Metabolic Surgery Is More than a Bariatric Surgery.* Obes Surg, 2019. **29**(9): p. 3001-3009.
9. Capristo, E., S. Panunzi, A. De Gaetano, V. Spuntarelli, R. Bellantone, P. Giustacchini, A.L. Birkenfeld, S. Amiel, S.R. Bornstein, M. Raffaelli, and G. Mingrone, *Incidence of Hypoglycemia After Gastric Bypass vs Sleeve Gastrectomy: A Randomized Trial.* J Clin Endocrinol Metab, 2018. **103**(6): p. 2136-2146.
10. Lee, C.J., T.T. Brown, M. Schweitzer, T. Magnuson, and J.M. Clark, *The incidence and risk factors associated with developing symptoms of hypoglycemia after bariatric surgery.* Surg Obes Relat Dis, 2018. **14**(6): p. 797-802.
11. Matthews, D.R., J.P. Hosker, A.S. Rudenski, B.A. Naylor, D.F. Treacher, and R.C. Turner, *Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man.* Diabetologia, 1985. **28**(7): p. 412-9.
12. Van Cauter, E., F. Mestrez, J. Sturis, and K.S. Polonsky, *Estimation of insulin secretion rates from C-peptide levels. Comparison of individual and standard kinetic parameters for C-peptide clearance.* Diabetes, 1992. **41**(3): p. 368-77.
13. Muka, T., M. Glisic, J. Milic, S. Verhoog, J. Bohlius, W. Bramer, R. Chowdhury, and O.H. Franco, *A 24-step guide on how to design, conduct, and successfully publish a systematic review and meta-analysis in medical research.* Eur J Epidemiol, 2020. **35**(1): p. 49-60.

14. Rethlefsen, M.L., S. Kirtley, S. Waffenschmidt, A.P. Ayala, D. Moher, M.J. Page, J.B. Koffel, and P.-S. Group, *PRISMA-S: an extension to the PRISMA Statement for Reporting Literature Searches in Systematic Reviews.* Syst Rev, 2021. **10**(1): p. 39.
15. Buser, A., C. Joray, M. Schiavon, C. Kosinski, B. Minder, C.T. Nakas, C. Dalla Man, T. Muka, D. Herzig, and L. Bally. *Effects of Roux-en-Y gastric bypass and sleeve gastrectomy on β-cell function at one year after surgery: a systematic review [Supplementary Material]*. 2022 25 Feb 2022; Available from: https://boris.unibe.ch/165875/.
16. Krentz Andrew J., H.L., Hompesch Marcus, *Translational Research Methods for Diabetes, Obesity and Cardiometabolic Drug Development*: Springer-Verlag London. 2015.
17. Bergman, R.N., L.S. Phillips, and C. Cobelli, *Physiologic evaluation of factors controlling glucose tolerance in man: measurement of insulin sensitivity and beta-cell glucose sensitivity from the response to intravenous glucose.* J Clin Invest, 1981. **68**(6): p. 1456-67.
18. Cobelli, C., C. Dalla Man, G. Toffolo, R. Basu, A. Vella, and R. Rizza, *The oral minimal model method.* Diabetes, 2014. **63**(4): p. 1203-13.
19. Mari, A., O. Schmitz, A. Gastaldelli, T. Oestergaard, B. Nyholm, and E. Ferrannini, *Meal and oral glucose tests for assessment of beta -cell function: modeling analysis in normal subjects.* Am J Physiol Endocrinol Metab, 2002. **283**(6): p. E1159-66.
20. Seltzer, H.S. and W.L. Smith, *Plasma insulin activity after glucose: an index of insulogenic reserve in normal and diabetic man.* Diabetes, 1959. **8**: p. 417-24.
21. Tura, A., B. Ludvik, J.J. Nolan, G. Pacini, and K. Thomaseth, *Insulin and C-peptide secretion and kinetics in humans: direct and model-based measurements during OGTT.* Am J Physiol Endocrinol Metab, 2001. **281**(5): p. E966-74.
22. Stumvoll, M., A. Mitrakou, W. Pimenta, T. Jenssen, H. Yki-Jarvinen, T. Van Haeften, W. Renn, and J. Gerich, *Use of the oral glucose tolerance test to assess insulin release and insulin sensitivity.* Diabetes Care, 2000. **23**(3): p. 295-301.
23. Kahn, S.E., R.L. Prigeon, D.K. McCulloch, E.J. Boyko, R.N. Bergman, M.W. Schwartz, J.L. Neifing, W.K. Ward, J.C. Beard, J.P. Palmer, and et al., *Quantification of the relationship between insulin sensitivity and beta-cell function in human subjects. Evidence for a hyperbolic function.* Diabetes, 1993. **42**(11): p. 1663-72.
24. Rohatgi, A. *WebPlotDigitizer*. August, 2021; 4.5:[Available from: https://automeris.io/WebPlotDigitizer.
25. Higgins JPT, T.J., Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors) *Cochrane Handbook for Systematic Reviews of Interventions version 6.2 (updated February 2021)*. Cochrane. 2021.
26. Higgins, J.P., D.G. Altman, P.C. Gøtzsche, P. Jüni, D. Moher, A.D. Oxman, J. Savovic, K.F. Schulz, L. Weeks, and J.A. Sterne, *The Cochrane Collaboration's tool for assessing risk of bias in randomised trials.* Bmj, 2011. **343**: p. d5928.
27. Sterne, J.A., M.A. Hernán, B.C. Reeves, J. Savović, N.D. Berkman, M. Viswanathan, D. Henry, D.G. Altman, M.T. Ansari, I. Boutron, J.R. Carpenter, A.W. Chan, R. Churchill, J.J. Deeks, A. Hróbjartsson, J. Kirkham, P. Jüni, Y.K. Loke, T.D. Pigott, C.R. Ramsay, D. Regidor, H.R. Rothstein, L. Sandhu, P.L. Santaguida, H.J. Schünemann, B. Shea, I. Shrier, P. Tugwell, L. Turner, J.C. Valentine, H. Waddington, E. Waters, G.A. Wells, P.F. Whiting, and J.P. Higgins, *ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions.* Bmj, 2016. **355**: p. i4919.
28. Dantas, W.S., H. Roschel, I.H. Murai, S. Gil, G. Davuluri, C.L. Axelrod, S. Ghosh, S.S. Newman, H. Zhang, S.K. Shinjo, W. das Neves, C. Merege-Filho, W.R. Teodoro, V.L. Capelozzi, R.M. Pereira, F.B. Benatti, A.L. de Sá-Pinto, R. de Cleva, M.A. Santo, J.P. Kirwan, and B. Gualano, *Exercise-Induced Increases in Insulin Sensitivity After Bariatric Surgery Are Mediated By Muscle Extracellular Matrix Remodeling.* Diabetes, 2020. **69**(8): p. 1675-1691.

29. Pournaras, D.J., J. Nygren, E. Hagström-Toft, P. Arner, C.W. le Roux, and A. Thorell, *Improved glucose metabolism after gastric bypass: evolution of the paradigm.* Surg Obes Relat Dis, 2016. **12**(8): p. 1457-1465.
30. Hofsø, D., F. Fatima, H. Borgeraas, K.I. Birkeland, H.L. Gulseth, J.K. Hertel, L.K. Johnson, M. Lindberg, N. Nordstrand, M. Cvancarova Småstuen, D. Stefanovski, M. Svanevik, T. Gretland Valderhaug, R. Sandbu, and J. Hjelmesæth, *Gastric bypass versus sleeve gastrectomy in patients with type 2 diabetes (Oseberg): a single-centre, triple-blind, randomised controlled trial.* Lancet Diabetes Endocrinol, 2019. **7**(12): p. 912-924.
31. Fatima, F., J. Hjelmesaeth, K.I. Birkeland, H.L. Gulseth, J.K. Hertel, M. Svanevik, R. Sandbu, M.C. Smastuen, B. Hartmann, J.J. Holst, and D. Hofso, *Gastrointestinal Hormones and beta-Cell Function After Gastric Bypass and Sleeve Gastrectomy: A Randomized Controlled Trial (Oseberg).* J Clin Endocrinol Metab, 2022. **107**(2): p. e756-e766.
32. Antonioli, L., D. Moriconi, S. Masi, D. Bottazzo, C. Pellegrini, M. Fornai, M. Anselmino, E. Ferrannini, C. Blandizzi, S. Taddei, and M. Nannipieri, *Differential Impact of Weight Loss and Glycemic Control on Inflammasome Signaling.* Obesity (Silver Spring), 2020. **28**(3): p. 609-615.
33. Astiarraga, B., L. Martínez, V. Ceperuelo-Mallafré, G. Llauradó, M. Terrón-Puig, M.M. Rodríguez, A. Casajoana, S. Pellitero, A. Megía, N. Vilarrasa, J. Vendrell, and S. Fernández-Veledo, *Impaired Succinate Response to a Mixed Meal in Obesity and Type 2 Diabetes Is Normalized After Metabolic Surgery.* Diabetes Care, 2020. **43**(10): p. 2581-2587.
34. Bojsen-Møller, K.N., C. Dirksen, N.B. Jørgensen, S.H. Jacobsen, A.K. Serup, P.H. Albers, D.L. Hansen, D. Worm, L. Naver, V.B. Kristiansen, J.F. Wojtaszewski, B. Kiens, J.J. Holst, E.A. Richter, and S. Madsbad, *Early enhancements of hepatic and later of peripheral insulin sensitivity combined with increased postprandial insulin secretion contribute to improved glycemic control after Roux-en-Y gastric bypass.* Diabetes, 2014. **63**(5): p. 1725-37.
35. Bose, M., J. Teixeira, B. Olivan, B. Bawa, S. Arias, S. Machineni, F.X. Pi-Sunyer, P.E. Scherer, and B. Laferrère, *Weight loss and incretin responsiveness improve glucose control independently after gastric bypass surgery.* J Diabetes, 2010. **2**(1): p. 47-55.
36. Camastra, S., E. Muscelli, A. Gastaldelli, J.J. Holst, B. Astiarraga, S. Baldi, M. Nannipieri, D. Ciociaro, M. Anselmino, A. Mari, and E. Ferrannini, *Long-term effects of bariatric surgery on meal disposal and β-cell function in diabetic and nondiabetic patients.* Diabetes, 2013. **62**(11): p. 3709-17.
37. Dutia, R., K. Brakoniecki, P. Bunker, F. Paultre, P. Homel, A.C. Carpentier, J. McGinty, and B. Laferrère, *Limited recovery of β-cell function after gastric bypass despite clinical diabetes remission.* Diabetes, 2014. **63**(4): p. 1214-23.
38. Franzini, M., V. Musetti, D. Guarino, L. Caponi, A. Paolicchi, M. Emdin, E. Ferrannini, and M. Nannipieri, *γ-Glutamyltransferase Fractions in Obese Subjects with Type 2 Diabetes: Relation to Insulin Sensitivity and Effects of Bariatric Surgery.* Obes Surg, 2018. **28**(5): p. 1363-1371.
39. Hofsø, D., T. Jenssen, J. Bollerslev, T. Ueland, K. Godang, M. Stumvoll, R. Sandbu, J. Røislien, and J. Hjelmesæth, *Beta cell function after weight loss: a clinical trial comparing gastric bypass surgery and intensive lifestyle intervention.* Eur J Endocrinol, 2011. **164**(2): p. 231-8.
40. Holter, M.M., R. Dutia, S.M. Stano, R.L. Prigeon, P. Homel, J.J. McGinty, Jr., S.J. Belsley, C.J. Ren, D. Rosen, and B. Laferrère, *Glucose Metabolism After Gastric Banding and Gastric Bypass in Individuals With Type 2 Diabetes: Weight Loss Effect.* Diabetes Care, 2017. **40**(1): p. 7-15.
41. Jørgensen, N.B., S.H. Jacobsen, C. Dirksen, K.N. Bojsen-Møller, L. Naver, L. Hvolris, T.R. Clausen, B.S. Wulff, D. Worm, D. Lindqvist Hansen, S. Madsbad, and J.J. Holst, *Acute and long-term effects of Roux-en-Y gastric bypass on glucose*

metabolism in subjects with Type 2 diabetes and normal glucose tolerance. Am J Physiol Endocrinol Metab, 2012. **303**(1): p. E122-31.
42. Khoo, C.M., J. Chen, Z. Pamuklar, and A. Torquati, *Effects of Roux-en-Y gastric bypass or diabetes support and education on insulin sensitivity and insulin secretion in morbidly obese patients with type 2 diabetes.* Ann Surg, 2014. **259**(3): p. 494-501.
43. Morínigo, R., A.M. Lacy, R. Casamitjana, S. Delgado, R. Gomis, and J. Vidal, *GLP-1 and changes in glucose tolerance following gastric bypass surgery in morbidly obese subjects.* Obes Surg, 2006. **16**(12): p. 1594-601.
44. Nannipieri, M., S. Baldi, A. Mari, D. Colligiani, D. Guarino, S. Camastra, E. Barsotti, R. Berta, D. Moriconi, R. Bellini, M. Anselmino, and E. Ferrannini, *Roux-en-Y gastric bypass and sleeve gastrectomy: mechanisms of diabetes remission and role of gut hormones.* J Clin Endocrinol Metab, 2013. **98**(11): p. 4391-9.
45. Nannipieri, M., A. Mari, M. Anselmino, S. Baldi, E. Barsotti, D. Guarino, S. Camastra, R. Bellini, R.D. Berta, and E. Ferrannini, *The role of beta-cell function and insulin sensitivity in the remission of type 2 diabetes after gastric bypass surgery.* J Clin Endocrinol Metab, 2011. **96**(9): p. E1372-9.
46. Nosso, G., E. Griffo, M. Cotugno, G. Saldalamacchia, R. Lupoli, G. Pacini, G. Riccardi, L. Angrisani, and B. Capaldo, *Comparative Effects of Roux-en-Y Gastric Bypass and Sleeve Gastrectomy on Glucose Homeostasis and Incretin Hormones in Obese Type 2 Diabetic Patients: A One-Year Prospective Study.* Horm Metab Res, 2016. **48**(5): p. 312-7.
47. Papamargaritis, D., C.W. le Roux, E. Sioka, G. Koukoulis, G. Tzovaras, and D. Zacharoulis, *Changes in gut hormone profile and glucose homeostasis after laparoscopic sleeve gastrectomy.* Surg Obes Relat Dis, 2013. **9**(2): p. 192-201.
48. Prasad, M., V. Mark, C. Ligon, R. Dutia, N. Nair, A. Shah, and B. Laferrere, *Role of the Gut in the Temporal Changes of beta-Cell Function After Gastric Bypass in Individuals With and Without Diabetes Remission.* Diabetes Care, 2022. **45**(2): p. 469-476.
49. Raverdy, V., G. Baud, M. Pigeyre, H. Verkindt, F. Torres, C. Preda, D. Thuillier, P. Gélé, M.C. Vantyghem, R. Caiazzo, and F. Pattou, *Incidence and Predictive Factors of Postprandial Hyperinsulinemic Hypoglycemia After Roux-en-Y Gastric Bypass: A Five year Longitudinal Study.* Ann Surg, 2016. **264**(5): p. 878-885.
50. Samat, A., S.K. Malin, H. Huang, P.R. Schauer, J.P. Kirwan, and S.R. Kashyap, *Ghrelin suppression is associated with weight loss and insulin action following gastric bypass surgery at 12 months in obese adults with type 2 diabetes.* Diabetes Obes Metab, 2013. **15**(10): p. 963-6.
51. Schrumpf, E., A. Bergan, O. Djøseland, O. Fausa, O. Flaten, D.W. Skagen, and B. Tronier, *The effect of gastric bypass operation on glucose tolerance in obesity.* Scand J Gastroenterol Suppl, 1985. **107**: p. 24-31.
52. Zetu, C., S.G. Popa, A. Popa, R. Munteanu, and M. Mota, *LONG-TERM IMPROVEMENT OF GLUCOSE HOMEOSTASIS AND BODY COMPOSITION IN PATIENTS UNDERGOING LAPAROSCOPIC SLEEVE GASTRECTOMY.* Acta Endocrinol (Buchar), 2018. **14**(4): p. 477-482.
53. Keidar, A., K.J. Hershkop, L. Marko, C. Schweiger, L. Hecht, N. Bartov, A. Kedar, and R. Weiss, *Roux-en-Y gastric bypass vs sleeve gastrectomy for obese patients with type 2 diabetes: a randomised trial.* Diabetologia, 2013. **56**(9): p. 1914-8.
54. Nemati, R., J. Lu, D. Dokpuang, M. Booth, L.D. Plank, and R. Murphy, *Increased Bile Acids and FGF19 After Sleeve Gastrectomy and Roux-en-Y Gastric Bypass Correlate with Improvement in Type 2 Diabetes in a Randomized Trial.* Obes Surg, 2018. **28**(9): p. 2672-2686.
55. Salehi, M., A. Gastaldelli, and D.A. D'Alessio, *Blockade of glucagon-like peptide 1 receptor corrects postprandial hypoglycemia after gastric bypass.* Gastroenterology, 2014. **146**(3): p. 669-680 e2.
56. Craig, C.M., H.M. Lawler, C.J.E. Lee, M. Tan, D.B. Davis, J. Tong, M. Glodowski, E. Rogowitz, R. Karaman, T.L. McLaughlin, and L. Porter, *PREVENT: A Randomized,*

Placebo-controlled Crossover Trial of Avexitide for Treatment of Postbariatric Hypoglycemia. J Clin Endocrinol Metab, 2021. **106**(8): p. e3235-e3248.
57. Akalestou, E., K. Suba, L. Lopez-Noriega, E. Georgiadou, P. Chabosseau, A. Gallie, A. Wretlind, C. Legido-Quigley, I. Leclerc, V. Salem, and G.A. Rutter, *Intravital imaging of islet Ca(2+) dynamics reveals enhanced beta cell connectivity after bariatric surgery in mice.* Nat Commun, 2021. **12**(1): p. 5165.
58. Elahi, D., P. Galiatsatos, A. Rabiee, R. Salas-Carrillo, A. Vakilipour, O.D. Carlson, F.S. Angeli, R.P. Shannon, J.M. Egan, and D.K. Andersen, *Mechanisms of type 2 diabetes resolution after Roux-en-Y gastric bypass.* Surg Obes Relat Dis, 2014. **10**(6): p. 1028-39.
59. Dirksen, C., K.N. Bojsen-Moller, N.B. Jorgensen, S.H. Jacobsen, V.B. Kristiansen, L.S. Naver, D.L. Hansen, D. Worm, J.J. Holst, and S. Madsbad, *Exaggerated release and preserved insulinotropic action of glucagon-like peptide-1 underlie insulin hypersecretion in glucose-tolerant individuals after Roux-en-Y gastric bypass.* Diabetologia, 2013. **56**(12): p. 2679-87.
60. Dirksen, C., A. Eiken, K.N. Bojsen-Moller, M.S. Svane, C. Martinussen, N.B. Jorgensen, J.J. Holst, and S. Madsbad, *No Islet Cell Hyperfunction, but Altered Gut-Islet Regulation and Postprandial Hypoglycemia in Glucose-Tolerant Patients 3 Years After Gastric Bypass Surgery.* Obes Surg, 2016. **26**(9): p. 2263-2267.
61. Salehi, M., A. Gastaldelli, and D.A. D'Alessio, *Beta-cell sensitivity to insulinotropic gut hormones is reduced after gastric bypass surgery.* Gut, 2019. **68**(10): p. 1838-1845.
62. Koopman, A.D.M., J.W. Beulens, A. van der Heijden, P. Elders, J.M. Dekker, M. Alssema, and F. Rutters, *A prospective study on glucagon responses to oral glucose and mixed meal and 7-year change in fasting glucose.* Clin Endocrinol (Oxf), 2019. **91**(1): p. 82-86.
63. Ferrannini, E. and A. Mari, *Beta cell function and its relation to insulin action in humans: a critical appraisal.* Diabetologia, 2004. **47**(5): p. 943-56.
64. Nemati, R., J. Lu, D. Dokpuang, M. Booth, L.D. Plank, and R. Murphy, *Increased Bile Acids and FGF19 After Sleeve Gastrectomy and Roux-en-Y Gastric Bypass Correlate with Improvement in Type 2 Diabetes in a Randomized Trial.* Obesity surgery, 2018. **28**(9): p. 2672-2686.
65. Dantas, W.S., H. Roschel, I.H. Murai, S. Gil, G. Davuluri, C.L. Axelrod, S. Ghosh, S.S. Newman, H. Zhang, S.K. Shinjo, W.D. Neves, C. Merege-Filho, W.R. Teodoro, V.L. Capelozzi, R.M. Pereira, F.B. Benatti, A.L. de Sá-Pinto, R. de Cleva, M.A. Santo, J.P. Kirwan, and B. Gualano, *Exercise-induced increases in insulin sensitivity after bariatric surgery are mediated by muscle extracellular matrix remodeling.* Diabetes, 2020. **69**(8): p. 1675-1691.
66. Breda, E., M.K. Cavaghan, G. Toffolo, K.S. Polonsky, and C. Cobelli, *Oral glucose tolerance test minimal model indexes of beta-cell function and insulin sensitivity.* Diabetes, 2001. **50**(1): p. 150-8.
67. Byrne, M.M., J. Sturis, K. Clement, N. Vionnet, M.E. Pueyo, M. Stoffel, J. Takeda, P. Passa, D. Cohen, G.I. Bell, and et al., *Insulin secretory abnormalities in subjects with hyperglycemia due to glucokinase mutations.* J Clin Invest, 1994. **93**(3): p. 1120-30.
68. Seltzer, H.S., E.W. Allen, A.L. Herron, Jr., and M.T. Brennan, *Insulin secretion in response to glycemic stimulus: relation of delayed initial release to carbohydrate intolerance in mild diabetes mellitus.* J Clin Invest, 1967. **46**(3): p. 323-35.
69. Tura, A., A. Kautzky-Willer, and G. Pacini, *Insulinogenic indices from insulin and C-peptide: comparison of beta-cell function from OGTT and IVGTT.* Diabetes Res Clin Pract, 2006. **72**(3): p. 298-301.
70. Boston, R.C., D. Stefanovski, P.J. Moate, A.E. Sumner, R.M. Watanabe, and R.N. Bergman, *MINMOD Millennium: a computer program to calculate glucose effectiveness and insulin sensitivity from the frequently sampled intravenous glucose tolerance test.* Diabetes Technol Ther, 2003. **5**(6): p. 1003-15.

71. Matsuda, M. and R.A. DeFronzo, *Insulin sensitivity indices obtained from oral glucose tolerance testing: comparison with the euglycemic insulin clamp.* Diabetes Care, 1999. **22**(9): p. 1462-70.
72. Retnakaran, R., S. Shen, A.J. Hanley, V. Vuksan, J.K. Hamilton, and B. Zinman, *Hyperbolic relationship between insulin secretion and sensitivity on oral glucose tolerance test.* Obesity (Silver Spring), 2008. **16**(8): p. 1901-7.
73. Kahn, S.E., *The relative contributions of insulin resistance and beta-cell dysfunction to the pathophysiology of Type 2 diabetes.* Diabetologia, 2003. **46**(1): p. 3-19.
74. Jensen, C.C., M. Cnop, R.L. Hull, W.Y. Fujimoto, S.E. Kahn, and G.S.G. American Diabetes Association, *Beta-cell function is a major contributor to oral glucose tolerance in high-risk relatives of four ethnic groups in the U.S.* Diabetes, 2002. **51**(7): p. 2170-8.

Figure Legends

Figure 1: PRISMA flowchart showing the process for the inclusion of studies.
* 28 articles referring to 27 studies (two articles (30, 31) both report results from the Oseberg-study)
Abbreviations: BCF, β-cell function; BMI, Body Mass Index

Figure 2: Effects of RYGB on BCF indices (a) and DI (b).

Illustration of individual effects of Roux-en-Y gastric bypass (RYGB) on indices of BCF.

Remark: some studies reported more than one index, this may lead to overrepresentation of the study in the figure which can lead to misinterpretation. DI calculation is denoted as a subscript (Panel 4b).

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. When results were only reported separately according to pre-surgery glucose tolerance, significance level was displayed separately, separated by "/" (non-diabetic/diabetic, or non-diabetic/pre-diabetes/diabetes as in Morinigo et al. (43))

Abbreviations: BCF, β-cell function; DI, disposition index; *NS, non-significant; NA, non-available.* Abbreviations for BCF indices are reported in Table 2 and Table 3.

Figure 3: Effect of SG on BCF indices (a) and DI (b)

Illustration of individual effects of sleeve gastrectomy (SG) on indices of BCF. DI calculation is denoted as a subscript (Panel 3b)

Remark: some studies reported more than one index, this may lead to overrepresentation of the study in the figure which can lead to misinterpretation.

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: BCF, β-cell function; DI, disposition index; NS, non-significant; NA, non-available. *Abbreviations for BCF indices are reported in Table 2 and Table 3.*

Figure 4: *Effect of RYGB vs. SG on BCF indices (a) and Disposition index (b).*

Comparison of the effects of Roux-en-Y gastric bypass (RYGB) and sleeve gastrectomy (SG) on indices of BCF (2a) and DI (2b). Remark: Some studies reported more than one index, this may lead to overrepresentation of the study in the figure which can lead to misinterpretation. DI calculation is denoted as a subscript (Panel 2b).

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: BCF, β-cell function; DI, disposition index; NS, non-significant; NA, non-available. *Abbreviations for BCF indices are reported in Table 2 and Table 3.*

Figure 5: *Effect of RYGB on BCF indices (a) and DI (b) according to pre-surgery diabetes status.*

Filling status of icons represents diabetes-status; filled icons are indicative non-diabetic individuals, half-filled icon re-present pre-diabetic individuals (impaired glucose tolerance) and empty icons represent type 2 diabetic subjects.

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: BCF, β-cell function; DI, disposition index; NS, non-significant; NA, non-available. *Abbreviations for BCF indices are reported in Table 2 and Table 3.*

		Author, Year	Reference	BCF evaluation	Modelling	Number of indices	BCF indices/DI	Follow up time (months)	Sample size (n)	Age (years)	Sex (% female)	BMI pre-surgery (kg/m^2)	BMI at follow up (kg/m^2)	Diabetes (*% baseline population*)
Randomised Controled Trial	**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	$\beta\text{-}GS_E$	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[b] SG 55 (44)/ 43[b]					100.0
		Keidar, 2013	(53)	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	(64)	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	**RYGB vs. SG**	Franzini, 2018	(38)	MMT	Mari A Model	1	$\beta\text{-}GS_M$	12	RYGB 21 SG 8	51.9±9.7	75.9	43.5±5.6	30.1±5.2	100.0
		Nannipieri, 2013	(44)	MMT	Mari A Model	2	$\beta\text{-}GS_M$, 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	(46)	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	(47)	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	(52)	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	(32)	OGTT	Mari A Model	1	$\beta\text{-}GS_M$	12	61	45.7±8.6	77.0	45.3±6.9	32.3±2.2	47.5
		Astiarraga, 2020	(33)	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	(34)	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	(35)	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	(36)	MMT	Mari A Model	2	$\beta\text{-}GS_M$, k_d	12	27 (21)*	NA	NA	52.2±7.3	35.0±5.6	44.4 (52.4)
		Dantas, 2020	(65)	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		OGTT	Empirical	3	$\beta\text{-}GS_E$, AUC isr/glu $_{0\text{-}180}$, $DI_{\beta\text{-}GS \times 1/HOMA\text{-}IR}$	12	16 (15) *	47.1±8.5	NA	43.9±4.9	30.3±3.7	100.0

		(37)	Iso-IVGC (Glucose matched to OGTT plasma glucose)		3	β-GS_E, AUC isr/glu $_{0-181}$, DI β-GS x 1/HOMA-IR						
	Hofso, 2011	(39)	OGTT	Empirical	4	IGI, AUC ins/glu $_{0-120}$, 1st PH, $DI_{1st\ PH\ x\ HOMA-S}$	12	64	53.3±9.2	70.3	47.3±5.7	33.1±5.3	46.9[c]
	Holter, 2017	(40)	OGTT	Empirical	4	β-GS_E, IGI, $DI_{IGI\ x\ Ismat}$, $DI_{IGI\ x\ 1/HOMA-IR}$	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, $DI_{AIR\ x\ Si}$							
	Jorgensen, 2012	(41)	MMT	Empirical	2	β-GS_E, $DI_{\beta-GS\ x\ 1/HOMA-IR}$	12	25 (24)*	47.7±11.3	60.0	42.3±5.1	32.6±6.7	52.0
	Khoo, 2014	(42)	insulin-modified IVGTT	Minimal Model	2	AIR, $DI_{AIR\ x\ Si}$	12	30	49.6±7.7	66.7	43.4±4.4	NA	100.0
	Morinigo, 2006	(43)	MMT	Empirical	1	AUC ins/glu $_{0-30}$	12	34	46.3±11.1	67.6	49.1±5.8	33.2±4.1	29.4 (35.3[d])
			IVGTT	Minimal Model	2	AIR, $DI_{AIR\ x\ 1/HOMA-IR}$							
	Nannipieri, 2011	(45)	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 $_{0-180}$	12	15	47.0±9.0	53.3	40.4±4.4	30.4±5.2	100.0
	Prasad, 2022	(48)	OGTT	Empirical	4	β-GS_E, IGI, AUC ins/glu 0-180 DI $_{\beta-GS\ x\ 1/HOMA-IR}$	12	36 (24)*	42.9±8.3	79.0	42.4±4.4	31.2±4.8	100.0
	Raverdy, 2016	(49)	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	(50)	MMT	Empirical	2	AUC ins/glu $_{0-30}$, AUC ins/glu $_{0-120}$, DI $_{AUC30\ x\ Ismat}$, DI $_{AUC120\ x\ Ismat}$	12	9	42.0±18.0	55.6	46.0±5.4	32.6±3.6	100.0
	Schrumpf, 1985	(51)	OGTT	Empirical	2	AUC ins/glu $_{0-180}$, AUC cp/glu $_{0-180}$	12	9	37.0±10.0	55.6	NA	NA	NA
			IVGTT		2	AUC ins/glu $_{0-180}$, AUC cp/glu $_{0-180}$							

Table 2. Overview of beta-cell function (BCF) indices reported in the included studies

Model/ Method			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	(66)	(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 $\Phi = \Phi_S + \frac{\Phi_D \cdot (G_{max} - G_b)}{\int_0^\infty [G(t) - h]dt}$		(9)
		Mari A Model	β-cell glucose sensitivity	$\beta\text{-}GS_M$	Beta-cell glucose sensitivity	pmol x min^{-1} x m^{-2} x mmol/L	Mean slope of the dose-response function f(G) (i.e., relationship between insulin secretion rates and plasma glucose concentrations during corresponding times of the test)	(19)	(32, 36, 38, 44, 45)
			Rate sensitivity	k_d	Dynamic control (pd)	pmol x m^{-2} x mmol/L nmol/m^2 [A]	Insulin secretory response to the positive rate of change in plasma glucose concentrations		(36, 44, 45)
	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	(67)	(31, 37, 40, 41, 48)
		Insulinogenic index	IGI with insulin	IGI	$Ins_{(30-0)}/Glc_{(30-0)}$	pmol/mmol [B] µIU x dL x mL^{-1} x mg^{-1} [C]	Δinsulin 0-30/Δglucose 0-30	(68, 69)	(33, 39, 40, 47-49, 53, 64) [D]
			IGI with C-peptide	IGI_{cp}		pmol/L/mM	ΔC-peptide 0-30/Δglucose 0-30		(34)
		AUC parameters	AUC insulin/ AUC glucose 0-30	AUC ins/glu_{0-30}	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]		(35, 43, 46, 50)
			AUC insulin/ AUC glucose total	AUC ins/glu_{0-120}	Total glucose-stimulated insulin release [J]	pmol/mmol	AUC insulin/AUC glucose $_{Tot}$ 0-120		(39, 47, 50)
				AUC ins/glu_{0-180}	AUC insulin glucose ratio [K] Total insulinogenic index (tIGI)	not reported	AUC insulin/AUC glucose $_{Tot}$ 0-180		(29, 48, 51)
			Insulin secretion index total	AUC isr/glu_{0-180}	AUC insulin secretion rate/ AUC glucose	pmol kg^{-1} $mmol^{-1}$	AUC-isr/AUC glucose 0–180		(37)
			AUC C-peptide/ AUC glucose total	AUC cp/glu_{0-180}	IGI 180*	nmol/pmol nmol/l/mg/dl [L,M]	AUC C-peptide/AUC glucose 0-180		(9, 46, 51)
				AUC $cp/glu_{0-180\ (abl)}$		nmol/pmol	AUC C-peptide/AUC glucose 0-180 (above basal levels)		(9)
		Stumvoll	First-phase insulin release	1st PH	Estimated first phase (first phase est)	pmol/l [N]	1,283 + 1.829 x $insulin_{30}$ - 138.7 x $glucose_{30}$ + 3.772 x $insulin_0$	(22)	(39, 47, 52)
			Second-phase insulin release	2nd PH	Estimated second phase (sampling times 0 and 30min)	pmol/l	286 + 0.416 x insulin 30 - 25.94 x glucose 30 + 0.926 x insulin 0		(52) [O]
IV procedures (IVGTT)	Empirical	**AIRg**			AUC overbasal insulin 0-10 min	(mU/L)*min[P]		(70)	
		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		(37, 40)
		AUC parameters	AUC Insulin/ AUC Glucose total	AUC ins/glu_{0-90}		.	AUC insulin/AUC glucose 0-90		(49)
			AUC C-peptide/ AUC glucose total	AUC cp/glu_{0-90}		.	AUC C-peptide/AUC glucose 0-90		(51)
			Insulin secretion index total	AUC isr/glu_{0-180}	ISX = AUC Insulin secretion rate/ AUC Glucose	.	AUC isr/AUC glucose 0–180		(37)

Abbreviations: IGI, insulinogenic index; IRI, Insulin Radio-Immunoassay; IVGTT, intravenous glucose tolerance test; MMT, mixed meal tolerance test; OGTT, oral glucose tolerance test

A: in Nannipieri 2011 and Camastra 2013; B: not reported in Nemati 2018, Papamargaritis 2013, Raverdy 2016; C: in Astiarraga 2020; D: calculation and time point are not specified in Nemati 2018; E: in Samat 2013; F: AUC insulin over AUC glucose was reported as IGI in Bose 2010; G: in Morinigo 2006; H: in Nosso 2016; I: unit not reported in Bose 2010 and Samat 2013; J: in Samat 2013; K: in Pournaras 2016; L: ISR for insulin secretion rate; M: in Nosso 2016; N: units are not reported in Schrumpf 1985; O: unit are not reported in Papamargaritis 2013; P: insulin was measured only at 0 and 30 min in Zetu 2018;

Table 3. Overview of the Disposition indices (DI) 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 x kg^{-1} x min^{-2}/pmol x L^{-1}	β-cell glucose sensitivity Φ x whole body insulin sensitivity S_i	(66)	(9)
	Empirical	$DI_{\beta\text{-GS} \times 1/HOMA\text{-}IR}$		-	β-GS x 1/HOMA-IR	(71, 72)	(37, 41, 48)
		$DI_{IGI \times ISmat}$	β-cell function index [Q]	-	IGI (Δinsulin 0–30 / Δglucose 0–30) x Matsuda index	(23, 71)	(40, 47, 65)
		$DI_{IGI \times ISclamp}$		-	IGI x insulin sensitivity (Rd_{clamp}/$insulin_{clamp}$) [R]	(73)	(34)
		$DI_{IGI \times 1/HOMA\text{-}IR}$		-	IGI x 1/HOMA-IR	(74)	(40)
		$DI_{AUC30 \times ISmat}$	β-cell function $_{0\text{-}30}$ / first phase oral disposition index	-	AUC Ins0–30/AUC Glc0–30 x Matsuda index		(50)
		$DI_{AUC120 \times ISmat}$	Oral dispostion index β-cell function 0-120 / total oral disposition index	-	AUC insulin 0–120/AUC glucose 0-120 x Matsuda index	(23)	(47, 50)
		$DI_{1st\ PH \times ISmat}$		-	first phase Stumvoll index x Matsuda index	(23)	(47)
		$DI_{1st\ PH \times HOMA\text{-}S}$		-	first phase Stumvoll index x HOMA-S	(23)	(39)
IV procedures (IVGTT)	**Model-based**	$DI_{AIR \times Si}$		-	AIRg x whole body insulin sensitivity Si	(70)	(30, 40, 42)
		$DI_{AIR \times 1/HOMA\text{-}IR}$	AIRg x 1/HOMA-IR [S]	-	AIRg x 1/HOMA-IR	(70)	(43)
	Empirical	$DI_{\beta\text{-GS} \times 1/HOMA\text{-}IR}$		-	β-GS x 1/HOMA-IR	(71, 72)	(37)

Abbreviations: DI, disposition index; IGI, insulinogenic index; IRI, Insulin Radio-Immunoassay; IS, insulin sensitivity; ISI, insulin sensitivity index; IVGTT, intravenous glucose tolerance test; MMT, mixed meal tolerance test; OGTT, oral glucose tolerance test

Q: unit reported as following in Khoo, 2014; R: referred with this nomenclature in Figures in Dantas 2020; S: Rate of disappearance (Rd) measured using a hyperinsulinemic-euglycemic clamp; T: not reported as disposition index

Figure 1

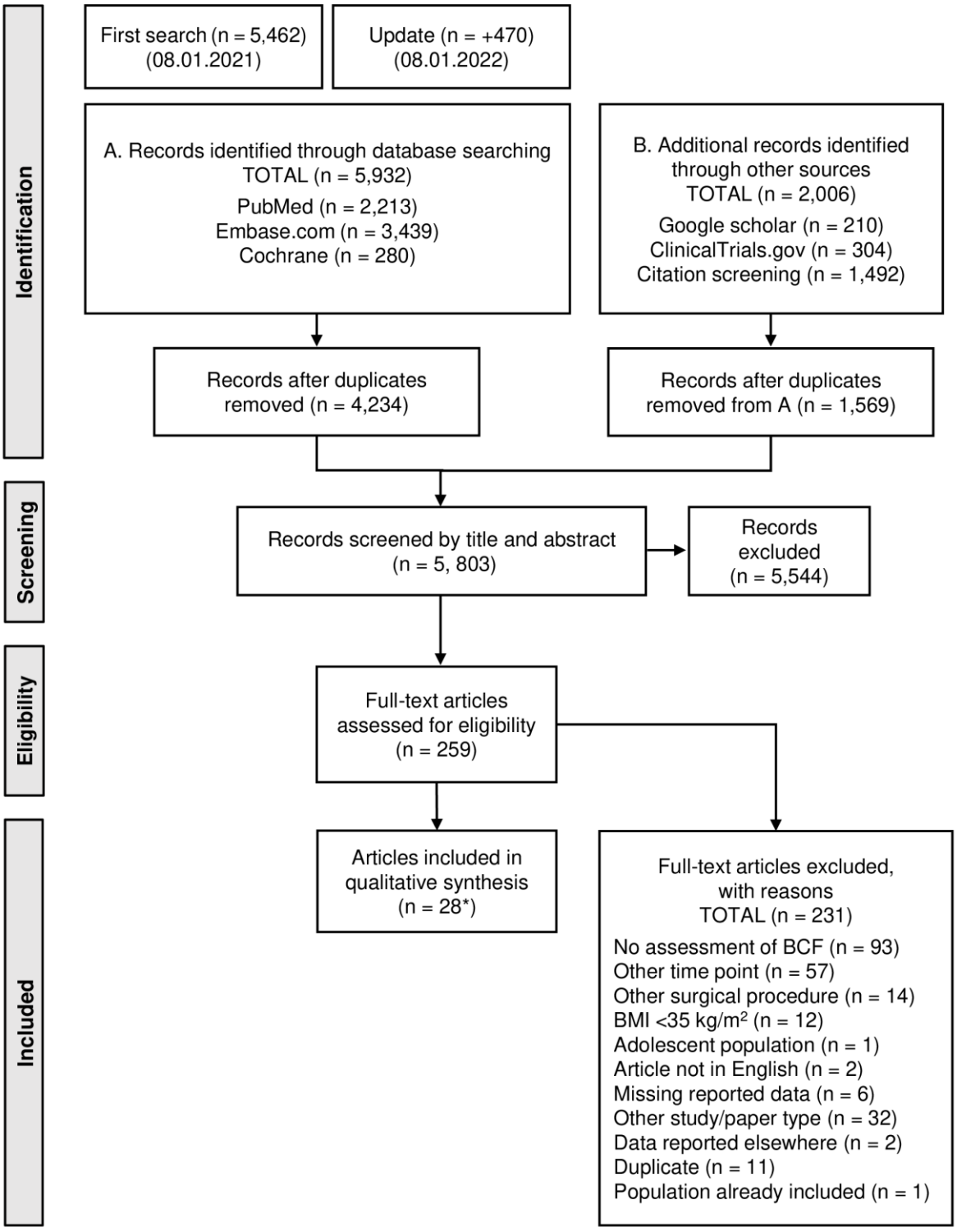

Figure 2

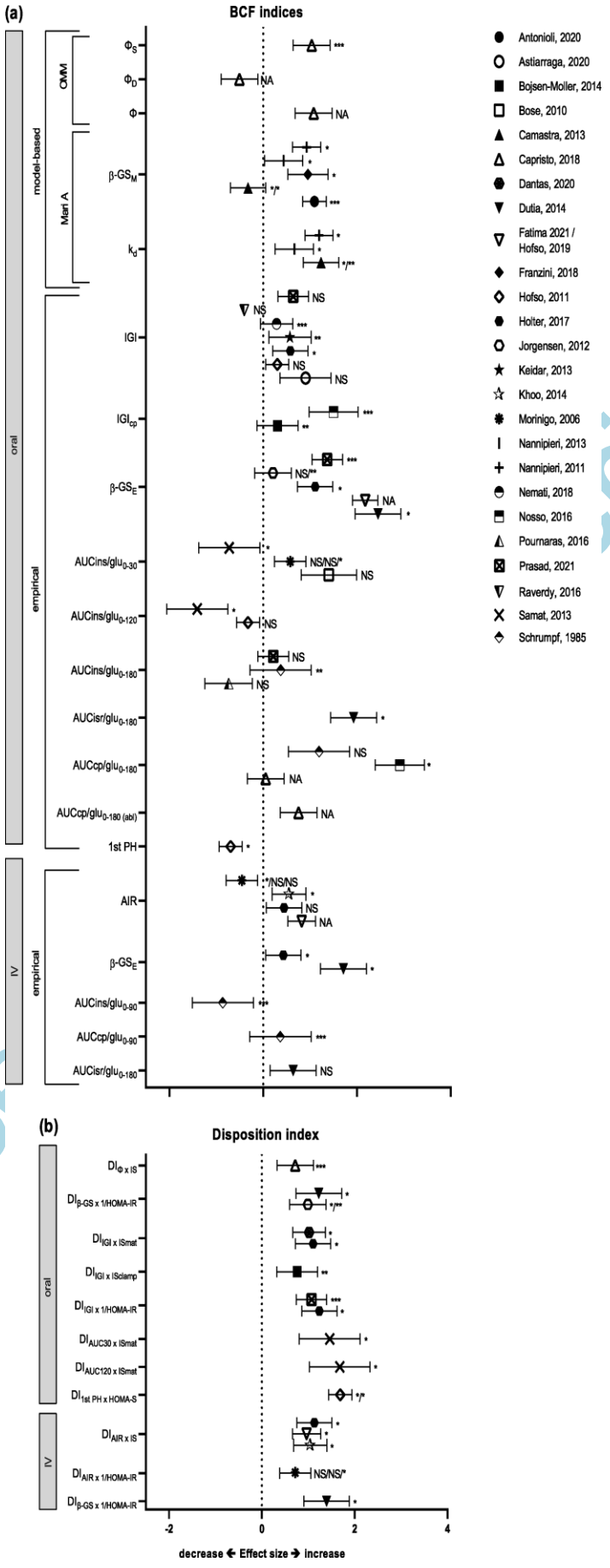

Figure 3

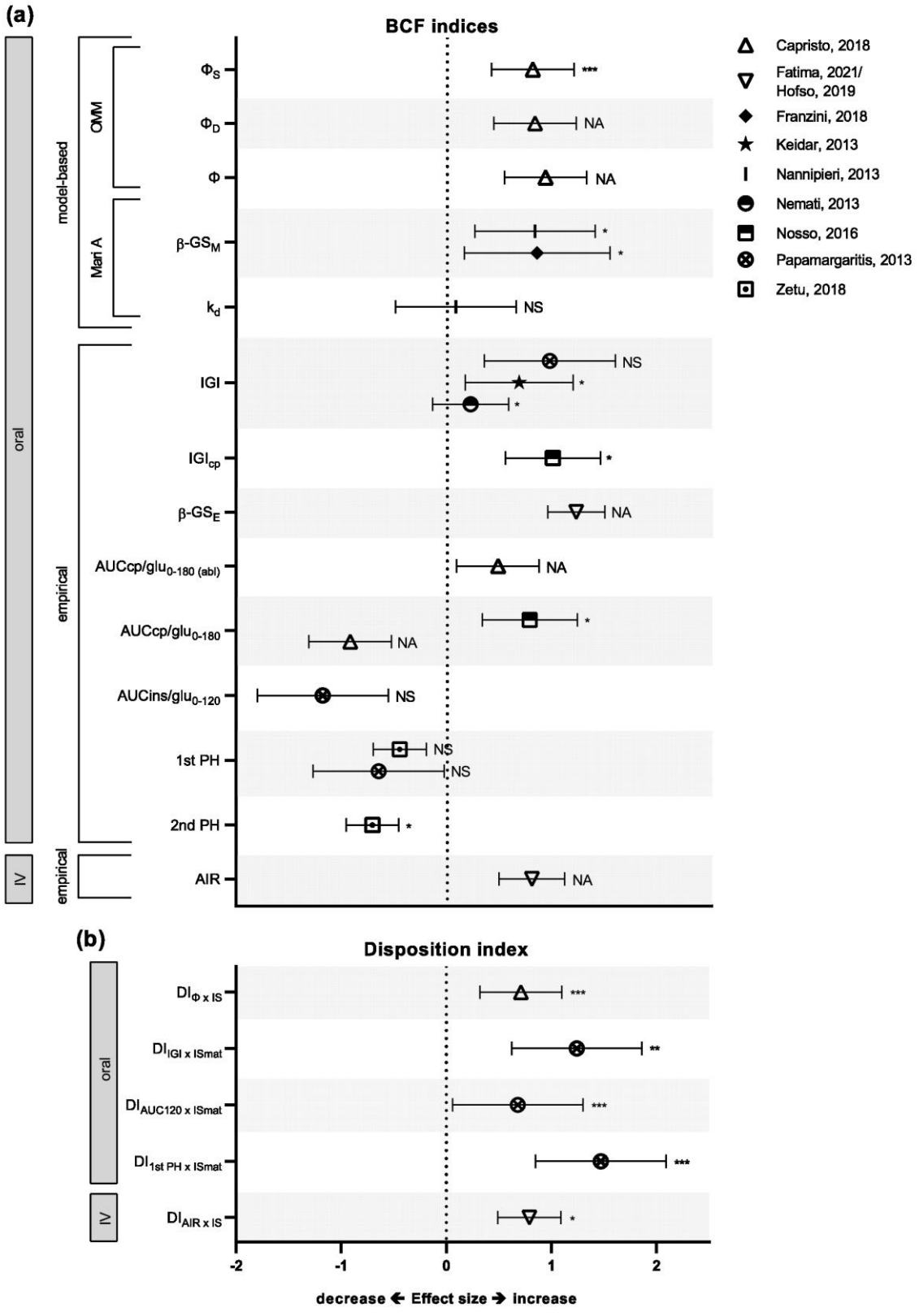

Figure 4

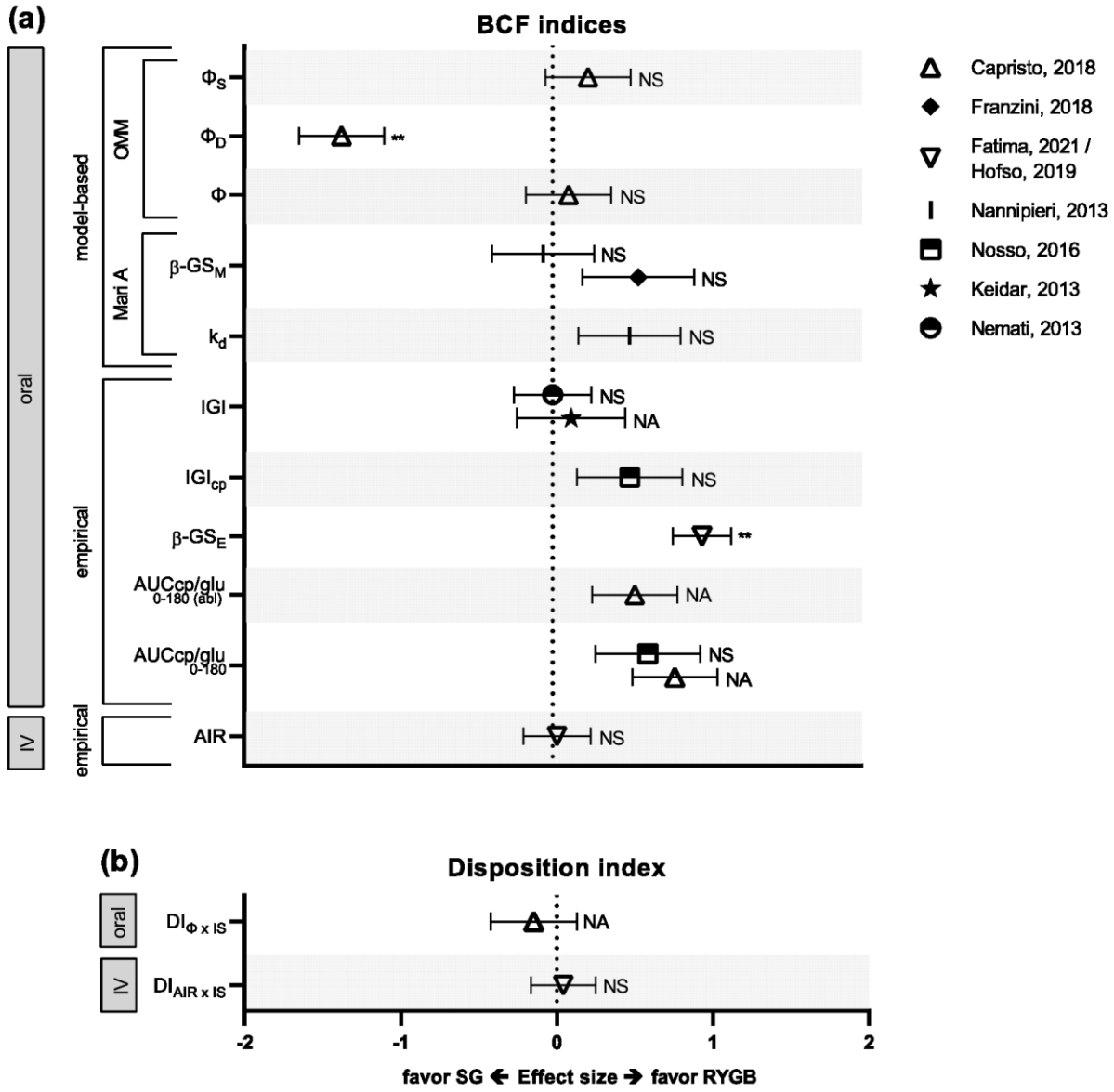

Figure 5