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REVIEW

Surgery-Induced Weight Loss and Changes in Hormonally Active Fibroblast Growth Factors: a Systematic Review and Meta-Analysis

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Abstract

This systematic review and meta-analysis was performed to investigate the possible changes of FGF-19 and FGF-21 after bariatric surgery (BS). Electronic databases including PubMed and Scopus were systematically searched up to February 2020 to identify pertinent studies. A total of 25 different studies were included. The overall pooled analysis identified that BS caused a significant increase in FGF-19, but had no significant effect on FGF-21. For FGF-19, this finding was supported in the subgroup analyses. For FGF-21, Roux-en-Y gastric bypass (RYGB) surgery significantly increased FGF-21 levels, whereas, in studies with follow-up duration ≥ 1 year, FGF-21 levels decreased significantly. BS reduces circulating concentration of FGF-19, but might increase FGF-21 after RYGB or decrease FGF-21 after ≥ 1 year.

Keywords Bariatric surgery · Obesity · Weight loss · Fibroblast growth factor · FGF-19 · FGF-21

Introduction

The prevalence of obesity has increased dramatically over the past decades worldwide representing a main threat for public health [1]. Obesity is accompanied by many metabolic complications such as endocrine dysregulations, insulin resistance, dyslipidemia, cardiovascular disease, nonalcoholic fatty liver disease, and subclinical inflammation resulting in a rise in morbidity and mortality [2]. Unfortunately, traditional approaches, such as diets and exercise, have not been so effective for the long-term management of weight, particularly in severe obese patients [3]. Bariatric surgery (BS) is presently the most effective therapeutic approach for severe obesity, yielding an improvement in its comorbidities, such as type 2 diabetes [2].

In addition to classical pathogenic factors, fibroblast growth factor 19 (FGF-19), the human ortholog of FGF-15 in the mouse, and FGF-21 are novel metabolically active hormones that have been intensively investigated given their therapeutic potential in obesity and metabolic recovery following BS, particularly for diabetes [4]. FGF-19 is produced primarily in enterocytes of distal ileum [5], while FGF-21 is secreted predominantly in the liver with lower secretion rates in the muscle, adipose tissue, and pancreas [6]. Both FGF-19 and FGF-21 are metabolic regulators of adiposity, energy homeostasis, and lipid and glucose metabolism [7, 8]. FGF-19 plays a crucial role in controlling bile acids [9]; decreasing food intake and brain-hedonistic responses [10]; and increasing fatty acid oxidation, insulin sensitivity, and energy expenditure [11]. Moreover, it has been shown that exogenous administration of FGF-19 or its overexpression reduces body weight and may have hypolipidemic and antidiabetic impacts [12, 13]. On the other side, FGF-21 is a powerful stimulator of glucose uptake and lipolysis in adipose tissue [14] with strong anti-steatosis [15], anti-inflammatory, antidiabetic, and hypolipidemic effects [16]. FGF-21 also plays a role in dietary macronutrient selection and regulating sweet taste preference [17, 18]. Accordingly, understanding changes in these hormones after surgery-induced weight loss has an important clinical value.

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Previous studies investigating the impact of the potential effect of weight loss caused by BS on circulating concentrations of FGF-19 and FGF-21 have reported inconclusive results, and this area of research is in debate. While several studies revealed significant favorable effects of BS on these hormones [16, 19, 20], other studies did not identify a significant effect [20, 21]. The disagreement among the literatures may be resulted from differences in the follow-up duration, surgery type, or baseline weight. Therefore, this systematic review and meta-analysis was performed to summarize the findings of previous studies and quantify the potential effect of BS on FGF-19 and FGF-21 levels based on the follow-up duration, baseline body mass index, and surgery type.

Methods

This meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement relevant to health care [22].

Search Strategy

The main databases, including PubMed and Scopus, were systematically searched on 20 February 2020 without any language restriction. The databases were searched using the following search strategy to find pertinent articles: (((((((((((((("Bariatric Surgery"[Majr]) OR "Bariatric Surgery"[Title/Abstract]) OR "Gastric Bypass"[Title/Abstract]) OR Gastrectomy[Title/Abstract]) OR "Biliopancreatic Diversion"[Title/Abstract]) OR Gastroplasty[Title/Abstract]) OR bariatric[Title/Abstract]) OR Roux-en-Y[Title/Abstract]) OR RYGB[Title/Abstract]) OR "Sleeve gastrectomy"[Title/Abstract]) OR "Gastric sleeve"[Title/Abstract]) OR "gastric band*"[Title/Abstract]) OR Lap-Band[Title/Abstract]) OR "duodenal switch"[Title/Abstract])) AND ((((((((("Fibroblast Growth Factors"[Mesh]) OR "fibroblast growth factors") OR "fibroblast growth factor") OR FGF) OR "fibroblast growth factor-19") OR FGF-19) OR "fibroblast growth factor-21") OR FGF-21) OR "fibroblast Growth Factor-23") OR FGF-23). Moreover, the reference lists of all included studies and pertinent reviews were manually scanned for additional relevant studies.

Inclusion and Exclusion Criteria

In the current meta-analysis, prospective non-randomized cohort studies and randomized clinical trials investigating the impacts of BS on fasting concentrations of FGF-19 and FGF-21 published up to February 2020 were included. Studies were included if (1) reported prospectively fasting concentrations of FGF-19 or FGF-21 pre-surgery and postsurgery, (2) the sample size was 8 or more, (3) the follow-up duration was at least 1 month, and (3) reported the study outcomes as mean ± standard deviation (SD) or sufficient information to calculate them. Studies were excluded if (1) assessed postprandial levels of outcomes after a meal ingestion; (2) assessed outcomes following a lifestyle weight loss program; (3) study duration was less than 1 month; (4) were case control or cross-sectional in design; (5) studies were reviews, animal or in vitro studies, editorials, and case reports. Besides, the studies by Kaválková et al. [23] and Nierop et al. [24], which assessed the effect of duodenal–jejunal bypass liner (DJBL) device implantation on FGF-19, were excluded because this technique is not a kind of BS. The titles/abstracts of all included publications were screened for assessing eligibility by the corresponding author (SH) and another investigator (AH) to check for consistency, after which each reviewer's included studies were compared and the measure of agreement was calculated using kappa statistic. Inter-rater agreement for selecting the studies for full-text review was excellent with a kappa score of 0.89, showing a high correlation between the two authors.

Data Extraction

With the use of a standardized data collection form, the following information was collected from each study: the first author's name, year of publication, country, background disease, patients' age and gender, sample size, type of BS, follow-up duration, and the mean ± SD of BMI, FGF-21 (pg/ml), and FGF-19 (pg/ml) before and after the BS. For some studies, data had been reported on figures; for these studies, data was extracted using the Plot Digitizer software. Data extraction was conducted independently by two investigators (AH and SH), and disagreements concerning data extraction were resolved by discussion until consensus reached.

Statistical Analysis

Since most included studies presented data as pg/ml, where data was presented as ng/ml or ng/dl, these were converted to pg/ml prior to analysis. Where data was reported as mean± standard error (SE), SE was converted to SD using the following formula: $SD = SE \times \sqrt{n}$ (n = sample size in each group). When data was reported as median ± interquartile range (IQR), assuming normal distribution of data, median was considered as mean, and SD was calculated as IQR/1.35. When endpoint means + SDs had not been reported but net changes from baseline (after–before) were reported, we calculated endpoint means as "net change + baseline mean" and SD was calculated with the use of the following formula using a correlation coefficient of 0.5 [25]: SD (difference) = [(SD2 (intervention) + SD2 (control) − 2 × 0.5 × SD (intervention) × SD (control)]$^{1/2}$. Pooled effect sizes in this meta-analysis were presented as weighted mean differences (WMD) and 95%

CI for outcomes. The heterogeneity across the studies was tested using I^2 statistic and was considered significant if $p < 0.1$ [26]. Because of the significant heterogeneity, the random-effects model was used to compare final values and baseline values of outcomes following BS. Moreover, subgroup analyses (by study duration, study population, baseline BMI) and meta-regression analyses (based on baseline BMI and follow-up period) were applied to find the sources of heterogeneity. The presence of publication bias was evaluated by Egger test and funnel plot [27]. Moreover, the overall quality of the evidence in each pooled analysis was evaluated with the use of the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) [28]. Meta-analysis was conducted by STATA software (version 13.0; StataCorp, College Station, TX, USA).

Results

Study Characteristics

The initial systematic search of databases found 275 studies. Of which, after removing 46 duplicate articles, 185 were excluded after scanning the titles/abstracts because they were irrelevant to the present meta-analysis. After carefully screening of 44 full texts, we also excluded 19 more studies because they assessed postprandial levels of outcomes after a meal test, used a lifestyle weight loss program, used duodenal–jejunal bypass liner device implantation, the duration was less than 1 month, or were case control studies in design, animal or in vitro studies, and reviews. Ultimately, a total of 25 different studies [9, 20, 29–51] with a total of 886 participants, published between 2011 and 2019, were eligible for the meta-analysis. The flow chart of study selection is presented in Fig. 1. Data obtained included 19 studies with 27 data sets on FGF-19 [9, 16, 19–21, 29–42] and 10 studies with 14 data sets on FGF-21 [6, 16, 34, 35, 40, 43–47]. The majority of the studies recruited obese patients without comorbidities [6, 16, 20, 31, 34–38, 43–45], while 4 studies reported their result for patients with type 2 diabetes mellitus (T2DM) diabetic and participants without T2DM separately (for these studies, we considered each study as 2 data sets) [21, 32, 40, 42], 7 studies were just performed on patients with T2DM [9, 19, 29, 30, 33, 39, 41], and 2 studies were on participants without T2DM [46, 47]. The sample size of the analyzed studies ranged between 8 and 115 participants. The follow-up duration of studies ranged from 1 to 24 months. The baseline BMI of participants ranged from 33.4 to 60.6. Patients underwent Roux-en-Y gastric bypass (RYGB) in 8 studies [9, 21, 30, 32, 35, 42, 44, 46] and sleeve gastrectomy (SG) in 8 studies [16, 19, 20, 31, 36, 38, 41, 45], while 4 studies reported their results for RYGB and SG separately [29, 34, 39, 47], and 1 study reported its result for RYGB and laparoscopic adjustable gastric banding (LAGB) separately [40]; for these studies, we considered each study as 2 data sets. The remaining procedures were duodenal diverted SG with ileal interposition (DDSG-II) [33], LAGB [37], laparoscopic greater curvature plication (LGCP) [43], and various surgery types [6]. Additionally, the sex of participants was not reported in 4 studies [35, 45–47], 1 article just included men [19], 3 articles just included women [16, 30, 40], and other ones involved both sexes. The characteristics of all included studies are presented in Table 1.

Findings from Meta-Analysis

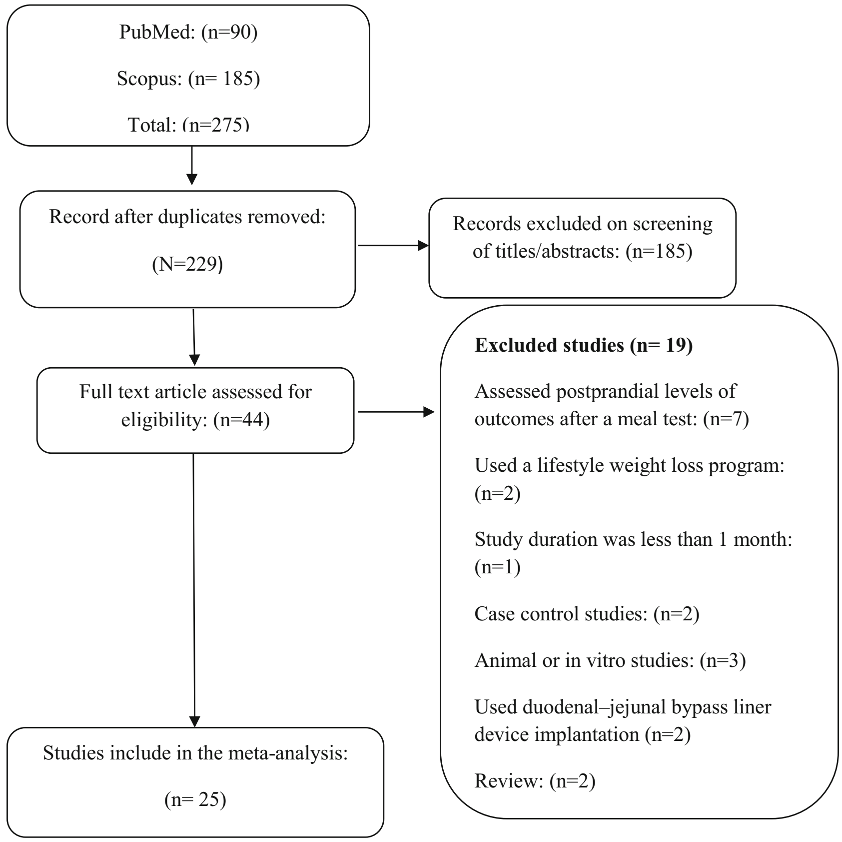
Bariatric Surgery and FGF-19

Among the included studies examining FGF-19 as an outcome, BMI decreased significantly by − 10.68 kg/m^2 following BS (Supplemental Fig. 1). Pooled effect size from 27 data sets, stratified by surgery type, overall revealed that the FGF-19 circulating levels increased significantly by 46.14 pg/ml following BS (WMD = 46.14, 95% CI 35.01 to 57.26; p = < 0.001), with a significant heterogeneity across studies (I^2 = 75.8%, p < 0.001). Both RYGB (WMD = 39.09, 95% CI 20.66–57.53) and SG (WMD = 62.55, 95% CI 46.07–79.03) significantly increased serum levels FGF-19; however, SG had a more potent effect on FGF-19 than RYGB (Fig. 2). In the subgroup analysis by follow-up duration (Supplemental Fig. 2 and Table 2), baseline BMI (Supplemental Fig. 3 and Table 2), sex of participants (Supplemental Fig. 4 and Table 2), and background disease (Supplemental Fig. 5 and Table 2), the mentioned increase in FGF-19 was observed too, except in obesity with other comorbidities but not T2DM, females, and patients undergoing other miscellaneous types of BS (n = 4 studies), which FGF-19 did not change significantly (Table 2).

Bariatric Surgery and FGF-21

In the studies that investigated changes in FGF-21 levels after BS, BMI decreased significantly by − 12.37 kg/m^2 following BS (Supplemental Fig. 6). Overall, when all data were pooled, BS had no significant effect on the serum levels of FGF-21(WMD = 70.80, 95% CI − 20.30 to 161.89; p = 0.12) and a significant evidence for heterogeneity was observed (I^2 = 90.30%, p < 0.001) (Fig. 3). Nevertheless, in the subgroup analysis by follow-up duration (Supplemental Fig. 7 and Table 2), baseline BMI (Supplemental Fig. 8 and Table 2), sex of participants (Supplemental Fig. 9 and Table 2), and background disease (Supplemental Fig. 10 and Table 2), it was found that RYGB is significantly related to increased FGF-21 levels (WMD = 188.84, 95% CI 6.85 to 370.83; p = 0.04), whereas, in studies with follow-up duration ≥ 1 year, FGF-21 levels decreased significantly following BS (WMD = − 41.27, 95% C − 70.74 to − 11.81; p = 0.006). Based on the

Fig. 1 Flow chart of the study



meta-regression analysis, follow-up time after BS was inversely related to FGF-21 levels in patients undergoing RYGB (β: − 78.96; SE: 13.26, $p = 0.004$) so that, by increasing time from surgery, the serum concentration of FGF-21 decreased. No significant effect in this regard was identified in other subgroups (Table 2).

Meta-Regression

Meta-regression analysis revealed that the levels of FGF-19 (β: 3.15; SE: 1.30, $p = 0.02$; Fig. 4a) and FGF-21 (β: − 22.40; SE: 10.60, $p = 0.05$; Fig. 4b) were modified by the follow-up time. Changes in FGF-19 (Supplemental Fig. 11) and FGF-21(Supplemental Fig. 12) were not affected by baseline BMI.

Publication Bias and Evaluation of Quality of Evidence According to the GRADE

There was no significant evidence of publication bias for studies examining the impact of BS on FGF-19 (Fig. 5a) and FGF-21 (Fig. 5b) based on Egger's linear regression test and by visual inspection of funnel plots. Using the GRADE system, the quality of the evidence across studies was classified as moderate for FGF-19, but the quality of the evidence was low for FGF-21 (Table 3).

Discussion

The present meta-analysis of available studies revealed that BS reduces serum levels of FGF-19, but might increase FGF-21 after RYGB or decrease FGF-21 after ≥ 1 year follow-up**.** Moreover, meta-regression analyses indicated that changes in FGF-19 and FGF-21 are affected by follow-up duration.

In addition to inconsistent findings of studies exploring the effect of BS on serum levels of FGF-19 and FGF-21, weight loss interventions using energy-restricted diets also have reported inconclusive results in this regard [34, 48, 49]. Mai et al. [49] identified that moderate weight loss (~ 5 kg) following a hypocaloric diet and physical activity for 6 months did not change FGF-21 concentrations in obese individuals. Moreover, Lips et al. [48] showed that a very low calorie diet is significantly related to an elevation in FGF-21 levels in obese patients with diabetes 3 weeks and 3 months after intervention. In another study [6], weight and adiposity decrease by an energy-restricted diet decreased serum levels of FGF-21, and weight recovery represented a tendency to raise FGF-21 or at least lessen its decrease. For FGF-19, fasting FGF-19 levels were unchanged after adherence to a low-calorie diet (800–1100 kcal per day) for 28 days in morbidly obese individuals [50]. Moreover, 3 weeks' intervention with a very low-calorie diet in obese subjects had no significant effect on FGF-19 in the study by Mráz et al. [51], which may be

Table 1 Study characteristics

Study	T2DM status (diabetes severity)	Year	Country	*n*	Sex (*n*)	Mean age	Surgery	Follow-up (months)	Pre-BMI (mean ± **SD**) (kg/m^2)	Post-BMI (mean ± **SD**)	Outcomes	
Haluzikova et al.	Obesity	2013	Czech Republic	17	Women (17)	39.9 ± 2.0	SG	24	43.2 ± 7	33.2 ± 7.83	FGF-19	FGF-21
Azevedo et al.	Type 2 diabetes (tablet-controlled)	2018	Brazil	10	Men (10)	45 ± 10	SG	3	33.4 ± 2.6	27.4 ± 2.8	FGF-19	–
Belgaumkar et al.	Obesity	2016	UK	18	Both (12 women, 6 men)	46.3 ± 2.9	SG	6	60.6 ± 7.77	45.8 ± 6.37	FGF-19	–
Chen et al.	Type 2 diabetes (patients receiving insulin, incretin hormone therapy, or diet-controlled T2DM were excluded)	2019	New Zealand	8	Both (16 women, 3 men)	42.9 ± 9.6	RYGB	3	43 ± 4.7	36.6 ± 4.3	FGF-19	–
				11		43.9 ± 6.7	SG	3	43.4 ± 6.1	37.4 ± 5.9	FGF-19	–
Dutia et al.	Type 2 diabetes (were not taking insulin and had A1C < 8%)	2015	USA	13	Women (13)	49.5 ± 8.5	RYGB	24	43.3 ± 4.9	29.9 ± 3.4	FGF-19	–
Escalona et al.	Obesity	2015	Chile	19	Both (15 women, 4 men)	37.6 ± 7.8	SG	12	35.8 ± 3.5	24.8 ± 6.2	FGF-19	–
Ferrannini et al.	Type 2 diabetes (were treated by diet, hypoglycemic tablets, and/or insulin)	2015	Italy	22	Both (11 women, 11 men)	49 ± 7	RYGB	14	48.8 ± 8.6	38.2 ± 6	FGF-19	–
	Without diabetes	2015	Italy	16	Both (15 women, 1 man)	44 ± 8	RYGB	13	53.5 ± 6.2	38.3 ± 5.4	FGF-19	–
Foschi et al.	Type 2 diabetes (not reported)	2015	Italy	12	Both (9 women, 3 men)	47 ± 3.2	duodenal diverted SG with ileal interposition (DDSG-II)	12	38.6 ± 2.2	26 ± 1.3	FGF-19	–
Gomez-Ambrosi et al.	Obesity	2017	Spain	20	Both (49 women, 37 men)	45.7 ± 13.3	SG	12	40 ± 6.5	29.6 ± 6.4	FGF-19	FGF-21
				66		41.3 ± 11.3	RYGB	12	45 ± 6.8	30.6 ± 4.6	FGF-19	FGF-21
Jansen et al.	Obesity	2011	The Netherlands	35	NR (35)	NR	RYGB	3	47.60 ± 5.2	NR	FGF-19	FGF-21
Jorgensen et al.	Without diabetes	2015	Denmark	12	Both (9 women, 3 men)	49–57	RYGB	12	44 ± 3.48	NR	FGF-19	–
	Type 2 diabetes (patients using antidiabetic medication and with diabetes duration ≥ 6 years)	2015	Denmark	13	Both (6	30–55	RYGB	12	41 ± 3.7	NR	FGF-19	–

Table 1 (continued)

Study	T2DM status (diabetes severity)	Year	Country	*n*	Sex (*n*)	Mean age	Surgery	Follow-up (months)	Pre-BMI (mean ± **SD**) (kg/m^2)	Post-BMI (mean ± **SD**)	Outcomes	
					women, 7 men)							
Salman et al.	Obesity	2019	Egypt	75	Both (35 women, 40 men)	43.63 ± 6.41	SG	6	43.37 ± 3.73	32.97 ± 2.75	FGF-19	–
Thoni et al.	Obesity	2017	Austria	20	Both (13 women, 7 men)	36.1	LAGB	12	43.5 ± 4.02	35.8 ± 7.15	FGF-19	–
Sachdev et al.	Type 2 diabetes (with diabetes duration at least ≥6 months before recruitment, hemoglobin A1c (HbA1c) levels of 8.0% or higher, and antidiabetic medication)	2015	USA	15	Both (7 women, 8 men)	46.9 ± 2.2	RYGB	12	36.2 ± 2.71	25.7 ± 3.45	FGF-19	–
Shimizu et al.	Obesity	2017	Japan	10	Both (5 women, 5 men)	48.8 ± 2.7	SG	6	40.9 ± 10.11	30.8 ± 3.16	FGF-19	–
Nemati et al.	Type 2 diabetes (with T2DM for at least 6-month duration)	2018	New Zealand	29	Both (31 women, 30 men)	47 ± 5	SG	12	40 ± 6.6	31 ± 6.6	FGF-19	–
				32		47 ± 1.2	RYGB	12	40 ± 0.7	29 ± 5.7	FGF-19	–
Lips et al.	Without diabetes	2014	The Netherlands	11	Women (27)	47.7 ± 1.3	LAGB	3	43.8 ± 0.6	NR	FGF-19	FGF-21
				16		47.7 ± 1.3	RYGB	3	43.8 ± 0.6	NR	FGF-19	FGF-21
	Type 2 diabetes (tablet-controlled)	2014	The Netherlands	15	Women (15)	51.0 ± 1.4	RYGB	3	42 ± 1.1	NR	FGF-19	FGF-21
Huang et al.	Type 2 diabetes (T2DM onset more than 6 months with glycated hemoglobin levels of 8% or higher and intensive medical care under an endocrinologist)	2019	Taiwan	18	Both (11 women, 7 men)	39.5 ± 8.9	SG	12	35.6 ± 5.1	27 ± 4.2	FGF-19	–
Gerhard et al.	Without diabetes	2013	USA	71	Both (68 women, 3 men)	46.2 ± 10.6	RYGB	12	48.2 ± 7	37.1 ± 6.5	FGF-19	–
	Type 2 diabetes (were prescribed an insulin sensitizer or insulin or combinations before surgery)	2013	USA	115	Both (97 women, 18 men)	50.9 ± 11.5	RYGB	12	49.02 ± 7.14	37.28 ± 5.87	FGF-19	–
Buzga et al.	Obesity	2015	Czech Republic	52	Both (33 women, 19 men)	24 to 68	Laparoscopic greater curvature	12	43.3 ± 10.6	33.3 ± 9.4	–	FGF-21

Table 1 (continued)

Study	T2DM status (diabetes severity)	Year	Country	*n*	Sex (*n*)	Mean age	Surgery	Follow-up (months)	Pre-BMI (mean ± **SD**) (kg/m^2)	Post-BMI (mean ± **SD**)	Outcomes	
							plication (LGCP)					
Fjeldborg et al.	Obesity	2017	Denmark	31	Both (19 women, 12 men)	44 ± 8	RYGB	12	42.5 ± 5.4	29.9	–	FGF-21
Khan et al.	Obesity	2016	USA	10	NR (10)	17.4 ± 0.5	SG	10	3	51.5 ± 7.9	NR	– FGF-21
Vienberg et al.	Without diabetes	2017	Denmark	NR	NR (NR)	NR	RYGB	NR	8	NR	NR	– FGF-21
Woelnerhanssen et al.	Without diabetes	2011	Switzerland	12	NR (24)	41.4 ± 2.9	RYGB	12	12	47.6 ± 6.92	31.1 ± 7.62	– FGF-21
				12		35.2 ± 3.2	SG	12	11	44.7 ± 5.3	32 ± 4.64	– FGF-21
Crujeiras et al.	Obesity	2017	Spain	25	Women (25)	NR	Various	25	1	>35	NR	– FGF-21

RYGB Roux-en-Y gastric bypass, *SG* sleeve gastrectomy, *LAG* laparoscopic adjustable gastric banding, *BMI* body mass index, *NR* not reported

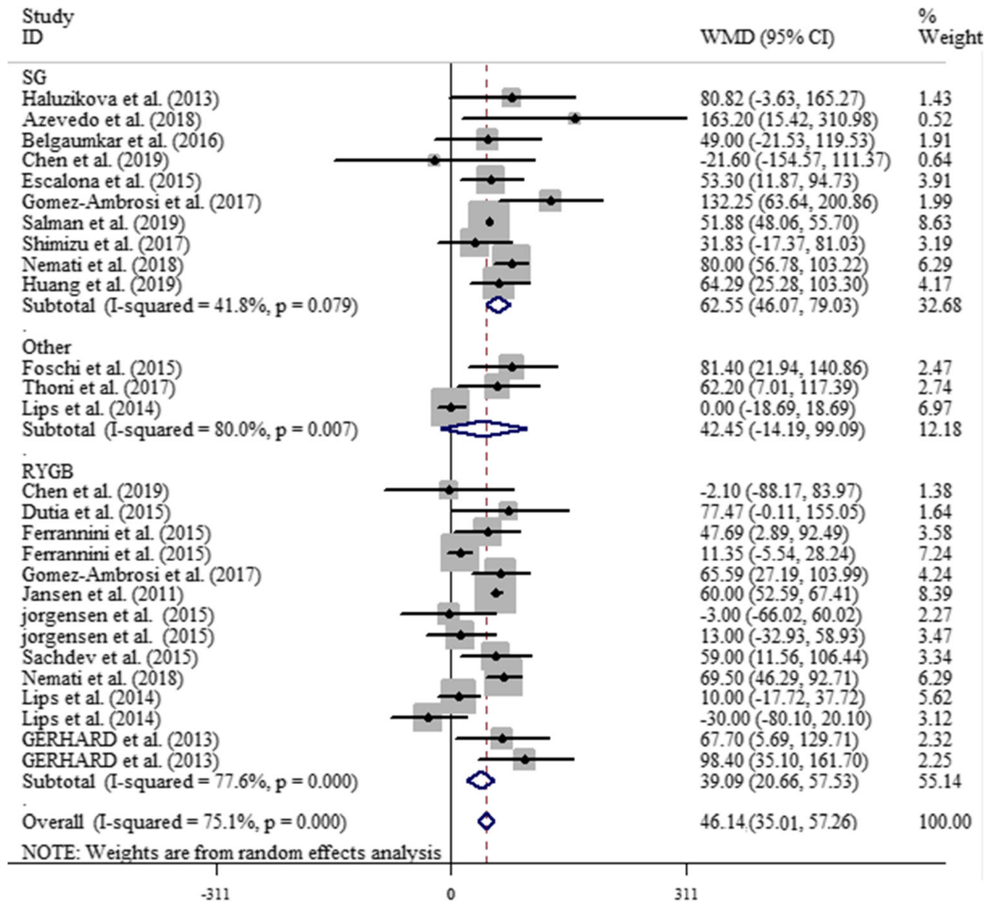


Fig. 2 Overall and stratified analysis by surgery type for the effect of bariatric surgery on the FGF-19 changes. SG sleeve gastrectomy, RYGB Roux-en-Y gastric bypass. Other: (duodenal diverted SG with ileal interposition (DDSG-II), laparoscopic adjustable gastric band (LAGB), laparoscopic greater curvature plication (LGCP), and various surgery types)

due to short follow-up duration and thus a negligible weight loss.

Increased FGF-19 concentrations and a long-term decrease in FGF-21 following BS observed in this meta-analysis could directly play a role in some of the positive metabolic changes of BS in obese patients. Both FGF-19 and FGF-21 have been shown to be involved in the etiopathology of type 2 diabetes and obesity, being potential therapeutic targets for the treatment of these metabolic complications [16]. They promote fatty acid oxidation; improve insulin sensitivity; increase metabolic rate; and, at pharmacological doses, induce weight loss and have hypolipidemic and antidiabetic impacts [52–55]. Studies have documented that FGF-19, as an endocrine hormone, represses cholesterol 7α-hydroxylase (CYP7A1) gene transcription and thus downregulates the synthesis and secretion of bile acids (BAs) [29]. FGF-19 appears to decrease Lp (a) production, a highly atherogenic particle [56], hereby reducing coronary artery disease severity [57]. Accordingly, one of the mechanisms for the remission of diabetes and metabolic diseases after BS may be mediated by improving FGFs.

It has been confirmed that serum levels of FGF-19 are reduced in obese patients, while FGF-21 concentrations are elevated in obesity, being further increased in obesity-related diabetes [34]. However, the expected beneficial effects of the paradoxically increase in FGF-21 in obesity are absent, which proposes that obesity is a FGF-21-resistant state [6]. Reduced FGF-21 levels ≥ 1 year after BS in our meta-analysis therefore might propose partial normalization of FGF-21 sensitivity, yielding a normalization and decrease in its circulating levels. Nevertheless, it is surprising to identify that FGF-21 level is elevated after RYGB. Following surgery, FGF-21 resistance is expected to be reduced quickly [35], and the observed elevation in serum level of FGF-21 after RYGB is to some extent conflicting to this. Some mechanisms might elucidate that FGF-21 level is not reverted following RYGB. First, RYGB can activate liver peroxisome proliferator-activated receptor a (PPARa) [48], which in turn increase the hepatic production of FGF-21 [58]. Second, significant alterations in intestinal hormones following RYGB could modulate FGF-21 concentrations [34]. Ultimately, RYGB might totally improve FGF-21 resistance [16], and a further elevation in FGF-21 concentrations may be a mechanism elucidating the better metabolic outcomes of RYGB over other bariatric surgeries. For instance, elevated FGF-21 concentrations and associated improvement in FGF-21 resistance will stimulate mitochondrial oxidation, thus playing a role in weight loss through a main pathway [35]. In high-fat diet/streptozotocin-induced diabetic rats, both duodenal–jejunal bypass and SG improved FGF-21

Table 2 Subgroup analyses for the effect of bariatric surgery on FGF-19 and FGF-21 concentrations

	Subgrouped by	No. of data sets	WMD[a] (95% CI)	p value[b]	I2 (%)[c]	p value[d]
FGF-19	Type of surgery					
	RYGB	10	39.09 (20.66–57.53)	< 0.001	77.6	< 0.001
	SG	14	62.55 (46.07–79.03)	< 0.001	41.8	0.07
	Other	3	42.42 (− 14.38 to 99.21)	0.14	80.3	0.006
	Follow-up period					
	< 1 year	10	29.10 (11.84–46.37)	0.001	85.4	< 0.001
	≥ 1 year	17	58.96 (41.64–76.28)	< 0.001	65.3	< 0.001
	Baseline BMI					
	< 45	20	44.73 (29.08–60.39)	< 0.001	75.4	< 0.001
	≥ 45	7	52.25 (27.41–77.08)	< 0.001	79.6	< 0.001
	Sex					
	Male	1	163.20 (15.42–310.98)	0.03	–	–
	Female	5	11.55 (− 15.14 to 38.23)	0.39	54.3	0.06
	Both	20	52.80 (40.20–65.41)	< 0.001	60.9	< 0.001
	Background disease					
	Obesity without comorbidities	9	55.93 (49.23–62.62)	< 0.001	22.4	0.24
	With diabetes	13	53.67 (32.88–74.46)	< 0.001	56.6	0.006
	Obesity with other comorbidities but not T2DM	5	8.66 (− 3.74 to 21.07)	0.17	13.6	0.32
FGF-21	Type of surgery					
	RYGB	7	188.84 (6.85–370.83)	0.04	93.9	< 0.001
	SG	4	− 78.10 (− 161.65 to 5.44)	0.06	40.9	0.16
	Other	3	34.12 (− 128.88 to 197.12)	0.68	87.2	< 0.001
	Follow-up period					
	< 1 year	6	288.81 (− 49.78 to 627.41)	0.09	93.1	< 0.001
	≥ 1 year	7	− 41.27 (− 70.74 to − 11.81)	0.006	10.8	0.34
	Baseline BMI					
	< 45	9	− 18.37 (− 85.53 to 48.80)	0.59	71.2	0.001
	≥ 45	4	228.11 (− 114.61 to 570.84)	0.19	96.5	< 0.001
	Sex					
	Female	4	2.46 (− 133.85 to 138.78)	0.97	51.4	0.10
	Both	5	− 13.74 (− 102.44 to 74.97)	0.76	81.8	< 0.001
	Background disease					
	Obesity without comorbidities	8	92.64 (− 51.66 to 236.94)	0.20	94.0	< 0.001
	With diabetes	1	280.00 (− 183.29 to 743.29)	0.23	–	–
	Obesity with other comorbidities but not T2DM	5	17.57 (− 80.82 to 115.97)	0.72	74.5	0.003

RYGB Roux-en-Y gastric bypass, *SG* sleeve gastrectomy

[a] Effect size was expressed as weighted mean difference

[b] For meta-analysis, $p < 0.05$ was considered to be a significant effect by using a random-effects model

[c] The I^2 statistic was calculated by using Cochran's test, and $I^2 > 50\%$ was considered to indicate significant heterogeneity across studies

[d] p value for I2

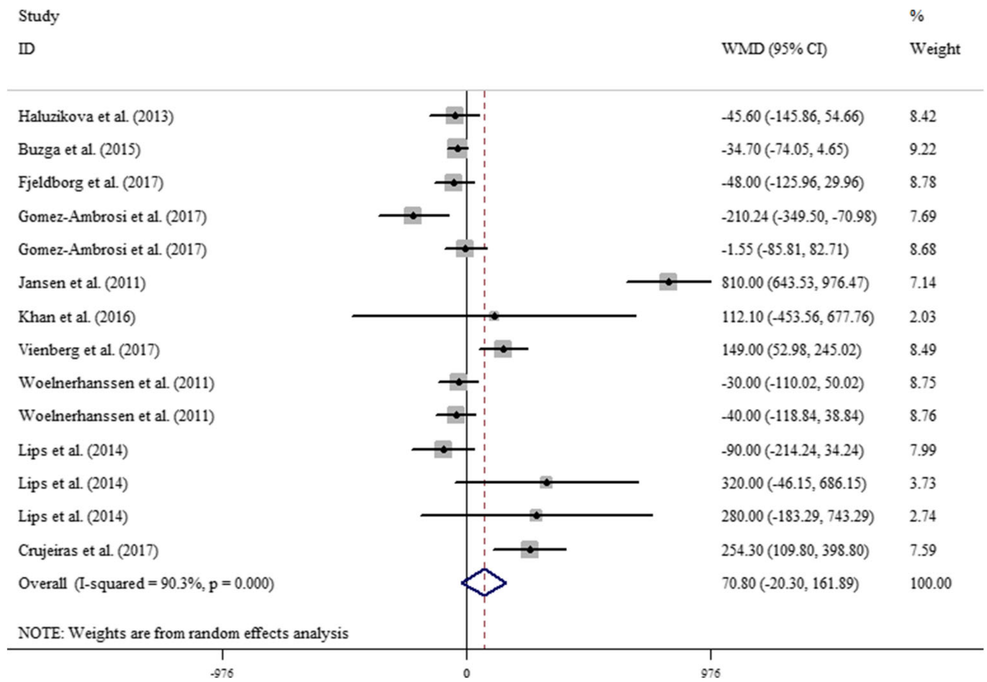


Fig. 3 Overall and stratified analysis by surgery type for the effect of bariatric surgery on the FGF-21 changes. SG sleeve gastrectomy, RYGB Roux-en-Y gastric bypass. Other: (duodenal diverted SG with ileal interposition (DDSG-II), laparoscopic adjustable gastric band (LAGB), laparoscopic greater curvature plication (LGCP), and various surgery types)

sensitivity and restored FGF-21 signaling pathway by increasing the expression of phosphorylated extracellular signal-regulated kinase 1/2 (ERK1/2) and FGF receptor 1 (FGFR1) 1 year after surgery [59]. Moreover, Fjeldborg et el. [44] revealed that beta-klotho (KLB) and FGF-R1 are upregulated in adipose tissue in human subjects undergoing RYGB surgery.

FGF-21 rises in metabolic stresses or after a rapid and massive weight or muscle loss, which mainly occurs during the first postoperative year after BS [6, 60]. Accordingly, at short time, FGF-21 should be only considered as a marker of metabolic stress [6]; nevertheless, we found no significant change in FGF-21 in studies with follow-up < 1 year. As FGF-21 concentration is tightly controlled nutritionally, one of the possible involving factors in reduced serum FGF-21 after a long-term weight loss (≥ 1 year) could be decreased food intake following BS [45]. This mechanism is supported by this observation that the FGF-21 levels are significantly decreased in chronically malnourished individuals with anorexia nervosa [16, 61]. On the other side, in subjects with obesity, the levels of BAs are low [62], but, after RYGB, serum BAs have been reported to be raised [35]; since FGF-19 is responsive to BAs, the increased FGF-19 concentrations might indeed be resulted from the increased levels of BAs [35]. Moreover, it has been found that, in patients with metabolic diseases, such as nonalcoholic fatty liver disease [63] and T2DM [64], serum level of FGF-19 is lower, while FGF-21 is higher in patients with diabetes compared with that in healthy individuals [65]. When serum concentrations of FGF-21 were > 500 mg/ml and FGF-19 < 200 mg/ml, 91% of patients had diabetes, suggesting that FGF-19/FGF-21 serum levels are remarkably dysregulated in T2DM and other obesity-related metabolic complications [65]. FGF-19 promotes glycogen synthesis and reduces gluconeogenesis, whereas concurrently decreasing triglyceride and cholesterol within the liver [66], all showing the clinical importance of increase in this hormone for the management of lipid and glycemic control in patients after BS. Thus, changes in the BAs-FGF-19 axis might involve the favorable metabolic alterations after BS. So et al. [67] recently published a meta-analysis focusing on change in bile acid metabolism following bariatric surgery and also analyzed 9 studies on FGF-19, which the results were in line with our finding. It should be considered that the study by So et al. included only 9 studies on FGF-19 while we included 19 studies with 27 data sets on this hormone. Therefore, we strongly believe that the recently published meta-analysis on FGF-19 has missed many eligible studies (missed 10 studies and analyzed 9 studies) and is potentially at risk of bias. Moreover, they did not assess changes in FGF-21 after bariatric surgery, and subgroup analysis for FGF-19 was not done. We performed analysis by the type of surgery, follow-up period, baseline BMI, sex, and background disease of participants and, as novel findings, found that the pooled effect sizes are significantly affected by these factors. Presently, our study is the most comprehensive meta-analysis on FGF-19 and the first meta-analysis on FGF-21.

As a strength point, no evidence for publication bias was observed. However, this meta-analysis had some limitations. First, there was a significant heterogeneity across the included

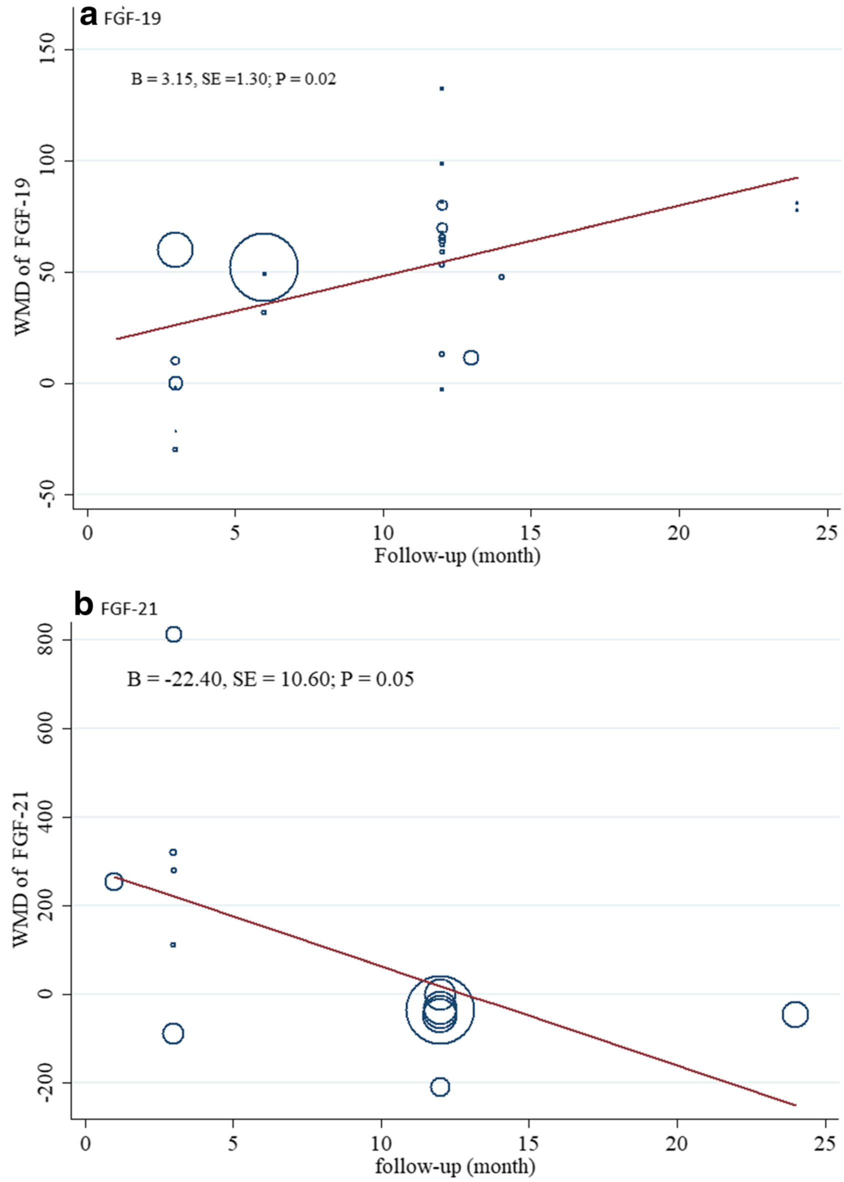


Fig. 4 Meta-regression analysis for the effect of bariatric surgery on FGF-19 (**a**) and FGF-21 (**b**) levels based on follow-up duration

publications; despite that, we used random-effects method to consider the heterogeneity. Our subgroup and meta-regression analyses found that surgery type, time of follow-up, background disease, and the sex of participants are potential sources of heterogeneity, suggesting that differences in these factors among various articles might partly justify the observed heterogeneity. Second, the included publications were generally observational case series and, thus, lack controls to consider any temporal variation in FGFs' concentrations that might exist. In fact, because of the severity of BS and its possible health complications, the majority of the analyzed articles reported a lack of ethical support from their organizations for a randomized clinical trial. Finally, however most studies recruited middle-age participants; one of the analyzed papers was performed on late adolescents (with a mean age of 17.4 year), and it is possible that the expression of FGFs in this population be different to that of the others. Nonetheless, we used the random-effects approach to control for such factors.

Future Directions

In addition to FGF-19 and FGF-21, it is well-known that FGF-23 has important metabolic roles; nevertheless, studies on the effects of metabolic surgery on the fibroblast growth factors have focused on serum FGF-19 and FGF-21. Therefore, future studies should also evaluate changes in FGF-23 following bariatric surgery. Furthermore, there are some studies on changes in postprandial peak or AUC in FGF-19 and FGF-21 levels that significant differences in these hormones may be found after

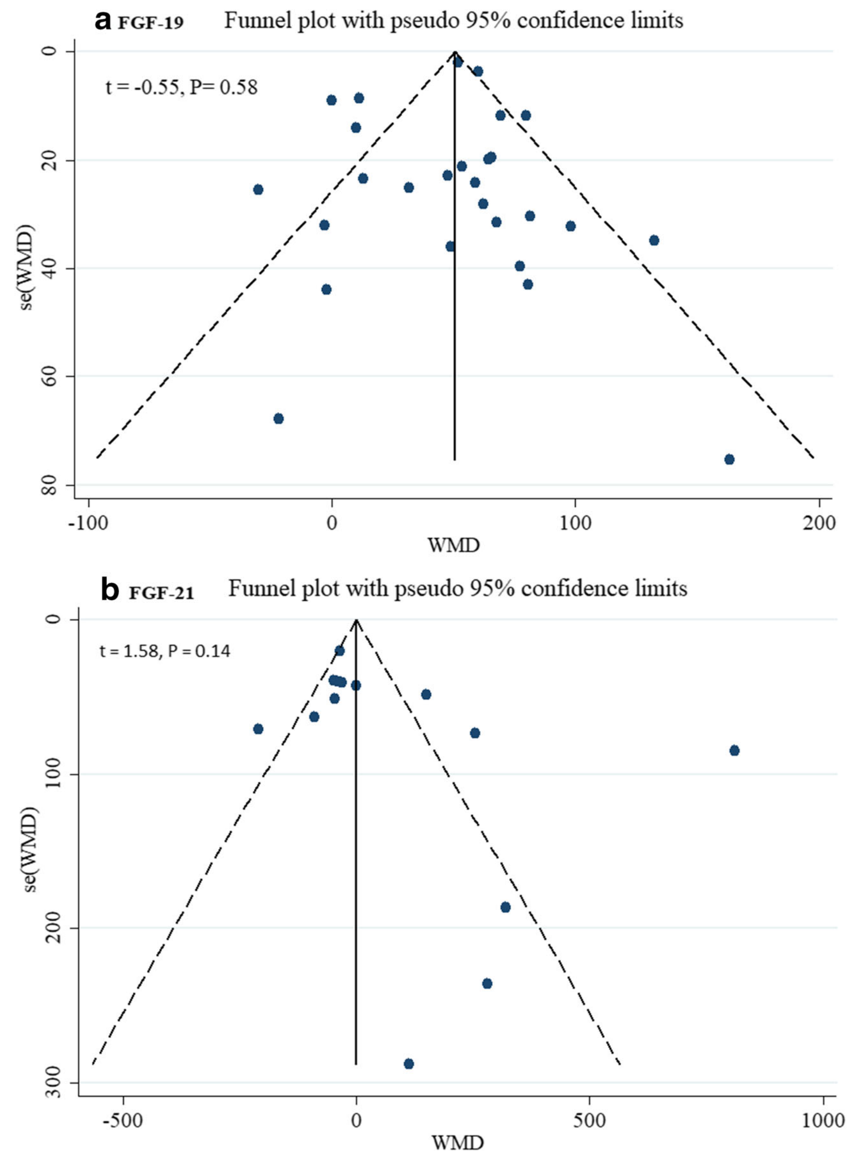


Fig. 5 Funnel plot for studies investigating the effect of bariatric surgery on FGF-19 (**a**) and FGF-21 (**b**) levels. WMD weighted mean difference, se (WMD) standard error for weighted mean difference

BS. Meta-analysis of postprandial peak in FGFs is recommended for future studies. Given that the included studies were prospective nonrandomized in design and that the quality of evidence for FGF-21 was low, future studies with randomized clinical trial could yield a more reliable result in this regard. Moreover, recognizing the molecular underpinnings of BS has a great significance, as this might reveal new drug targets for more durable and potent medical treatments. FGF-19 and FGF-21 could be candidates for such targets. The impacts of single-hormone therapies have been disappointing occasionally, and thus, some researchers are presently concentrating on developing a combination therapy of hormones. For instance, the levels of the gut hormones peptide YY, glucagon-like peptide 1 (GLP-1), and oxyntomodulin all are increased in response to RYGB [68] and were recently combined as a subcutaneous injectable therapeutic in a clinical trial of obese patients with T2DM and compared against a very low-calorie diet, RYGB, and placebo [69]. This combined therapy resulted in a remarkable improvement in insulin sensitivity, which was akin to that of RYGB, although the weight loss induced by the therapeutic was about half that of the RYGB group after 4 weeks of surgery. Considering findings reported herein, it might be valuable to investigate the effectiveness of a quadruple-hormone therapy for diabetes and obesity, combining FGF-19 or FGF-21 with the three previously hormones in the future studies.

Conclusions

Our pooled analyses provided evidence that significant weight loss after BS reduces serum levels of FGF-19 but might

Table 3 Quality of evidence based on the GRADE scale

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Pre-surgery	Postsurgery	Relative (95% CI)	Absolute	Quality	Importance
FGF-19												
19	Prospective non-Randomized trials	No serious risk of bias	Serious [a]	No serious	No serious	None	719	719	–	WMD = 46.14, (95% CI: 35.01–57.26)	⊕⊕⊕O Moderate	Critical
FGF-21												
10	Prospective nonrandomized trials	No serious risk of bias	Serious [a]	No serious	Serious [b]	None	347	347	–	WMD = 70.80, (95% CI: − 20.30 to 161.89)	⊕⊕OO Low	Critical

[a] Significant heterogeneity; [b] Wide confidence interval and low sample size

increase FGF-21 after RYGB or decrease FGF-21 after ≥ 1 year of follow-up. Since morbidly obese people are at high risk for metabolic diseases and these biomarkers are associated with an improvement in metabolism, the results found in this meta-analysis could have clinical values for morbidly obese people undergoing BS.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Ethical Approval For this type of study, formal consent is not required.

Informed Consent Statement Informed consent does not apply.

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