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Bariatric surgery following treatment for craniopharyngioma: a systematic review and individual-level data meta-analysis

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Objectives: Craniopharyngiomas are rare low-grade tumors located in the hypothalamic or/and the pituitary region. Hypothalamic involvement and treatment resulting in hypothalamic damage are known to lead to development of "hypothalamic" obesity (HyOb) in 50% of cases. The management of HyOb, associated with eating disorders and rapid comorbidities, is an important issue. Bariatric surgery is the most effective therapy for weight loss in patients with severe exogenous obesity. The aim of this systematic review and meta-analysis was to determine the 12 month outcome of bariatric surgery for HyOb due to craniopharyngioma treatment.

Methods and Results: Relevant studies were identified by searches of the MEDLINE and EMBASE databases until January 2013. A total of 21 cases were included: 6 with adjustable gastric banding, 8 with sleeve gastrectomy, 6 with Roux en Y gastric bypass, and 1 with biliopancreatic diversion. After data pooling, mean weight difference was -20.9 kg after 6 months [95% CI: - 35.4, -6.3] and -15.1 kg after 12 months [95% CI: -31.7, +1.4]. The maximal mean weight loss was achieved by the gastric bypass group: -31.0 kg [95% CI: -77.5, +15.5] and -33.7 kg [95% CI: -80.7, +13.3] after 6 and 12 months, respectively.

Conclusions: In this largest ever published study on the effect of bariatric surgery on obesity following craniopharyngioma treatment, we observed an important weight loss after one year of follow-up. Larger studies are warranted to establish appropriate selection criteria and the best surgical technique to perform bariatric surgery.

Craniopharyngiomas are benign slow growing tumors that are located within the sellar and parasellar region of the central nervous system (CNS). There are two histological types: the adamantinomatous tumors, mostly seen in children, which arises from epithelial remnants of the Rathke's pouch; and the squamous papillary form seen in adults. The incidence rate ranges from 0.5 to 2/ 1.000 000 subjects/y, with a peak between 5 and 14 y old, although craniopharyngiomas can occur at any age (1).

Tumor resection, with or without radiotherapy, represents the therapeutic standard of care. Following treatment, obesity and eating disorders are observed in 40%–50% of patients (2, 3, 4). Weight gain is also observed at diagnosis before treatment in some patients. Risk factors for the development of obesity after treatment of craniopharyngioma include younger age at diagnosis, presence of endocrinopathy whatever type, initial symptoms of intracranial hypertension, greater body mass index (BMI) at diagnosis, familial predisposition for obesity and hypothalamic involvement. In addition, pterional surgery, multiple surgery and hypothalamic irradiation with doses greater than 51 Gy have been associated with the development of obesity (3, 5, 6, 7).

The cause of weight gain in this setting is incompletely understood, but is believed to be due to "endogenous" mechanisms, rather than the more common form of "exogenous" obesity that is not related to acquired disruption of internal energy balance mechanisms. Briefly, the most common hypotheses include damage of satiety centers within the hypothalamus, hypersecretion of insulin induced by vagal disinhibition, hormonal deficiencies, and also interruption of catabolic pathways in the hypothalamus leading to decreased physical activity related energy expenditure (8). All these mechanisms are plausible, based on the location or treatment of the tumor. Several medical treatment options have been explored in patients with "hypothalamic" obesity (HyOb), such as the use of adrenergics to enhance and mimic sympathetic activity (9, 10, 11, 12), or lowering of insulin secretion with hypoglycemic agents such as octreotide or diazoxide (13, 14). The degree of weight control achieved by these pharmacotherapies or with lifestyle modification is typically modest and often transient (15, 16, 17). In adults with exogenous obesity, bariatric surgery has proven to be the most effective therapy for severe obesity in terms of weight loss, reduction in morbidity and mortality and improvement of quality of life (QOL) (15, 18, 19). Far less is known about the outcome of bariatric surgery in those with eating disorders and deficient modulation of satiety characteristic of HyOb.

Several case reports were published in the literature describing the use of bariatric surgery for HyOb (20); however aggregated larger numbers are needed to better understand the real potential of such treatment in patients with craniopharyngioma. We therefore conducted a systematic review and meta-analysis of individual data on the impact of bariatric surgery on weight loss for HyOb in patients with craniopharyngioma.

Materials and Methods

Data sources and searches

We performed a systematic review of available literature according to the MOOSE guidelines (21) to investigate the impact of bariatric surgery on weight loss in individuals with neurosurgically-treated craniopharyngioma. Relevant articles published in English until January 2013 were identified from MEDLINE and EMBASE using combined text and MeSH heading search strategies (Webtable 1). References listed in articles of interest were then scrutinized and experts in the field were contacted to identify additional relevant cases studies.

Study selection

Studies were included if they had provided quantitative estimates (including variability) of weight at 6 and/or 12 mo after bariatric surgery. In the case of duplicates, we included the most recent publication. Studies that were not published as full reports, such as conference abstracts or letters to editors, were excluded.

Titles of all articles retrieved from database searches were screened for relevance based on whether the study investigated anthropometric outcomes following bariatric surgery. The abstracts of articles scored as relevant were examined and full manuscripts for all eligible studies were retrieved. References from these studies and previous reviews were also examined for any other relevant articles. The literature search was conducted by two authors (M.B. and S.C.); scoring of relevance was concordant.

Data extraction and quality assessment

Due to the heterogeneity of follow-up periods, uniformity of data collection for this study required contact of corresponding authors for studies eligible for meta-analysis. Contact was made by electronic mail and authors were invited to participate in this study and asked to complete a standardized data extraction form characterizing their cases, including craniopharyngioma and bariatric surgery characteristics, and anthropometric features before and after bariatric surgery.

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Abbreviations:

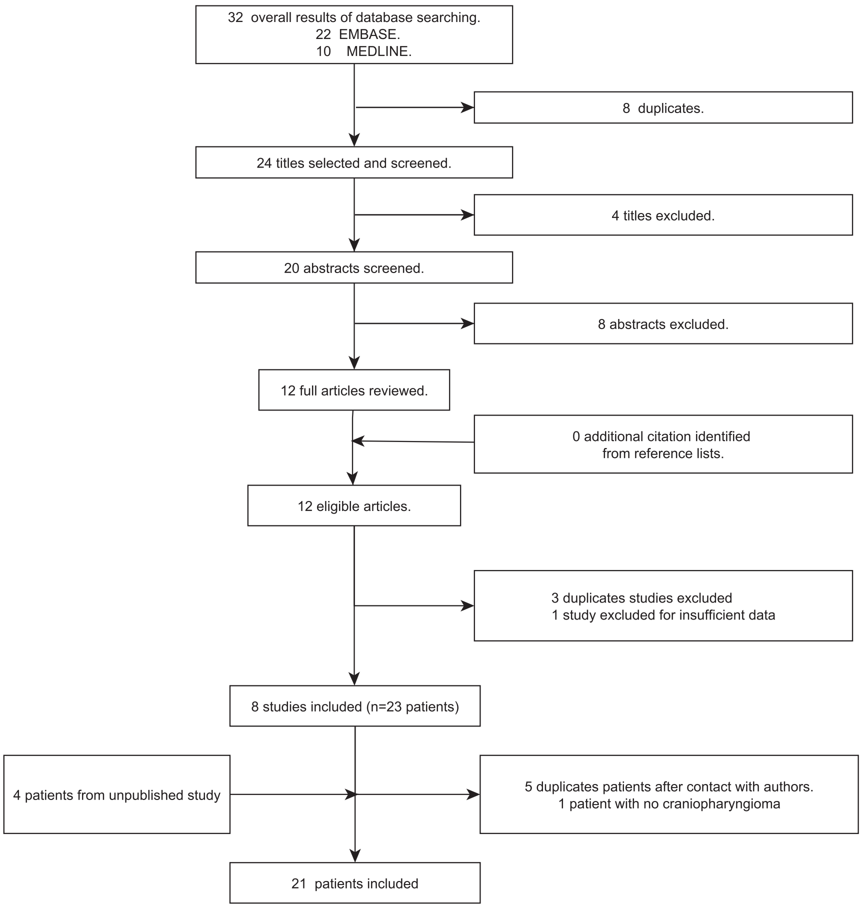

Figure 1. Flow-chart identifying eligible studies

Data synthesis and analysis

We compared the percent change in weight between baseline and 6 and 12 mo after surgery across bariatric procedure types. Moreover, changes in weight were also plotted for individual cases. Data were pooled to compare evolution in weight across bariatric surgery procedures (laparoscopic adjustable gastric banding [LAGB], Roux en Y gastric bypass [RYGB], sleeve gastrectomy [SG], and biliopancreatic diversion [BPD]) using mean differences (MD) at 6 and 12 mo with weight at the time of bariatric surgery as the reference. The inverse variance method with random effects was used (22). The percentage of variability across studies attributable to heterogeneity rather than chance was estimated using the I2 statistic (23). All analyses were performed using R (R, version 2.12.1, the R Core Development team, 2010) and Review Manager (RevMan, version 5.0, The Cochrane Collaboration, 2008).

Results

Study selection

The search strategy identified a total of 32 studies (Figure 1). Twenty studies were excluded: 8 duplicates, 4 because of irrelevant titles and 8 after reading the abstracts. Three articles reported data from the same cohort and were also excluded. One more article was excluded because of the lack of anthropometric data. Eight articles were finally selected and a standardized questionnaire was sent to each author in order to collect individual data pertaining to each case described in the studies that had been identified (12, 24, 25, 26, 27, 28, 29, 30). All contacted authors contributed to the meta-analysis. One author (H. L. Müller) completed the standardized adding data of one unpublished case. We also contributed to the meta-analysis by adding unpublished data from 3 patients followed-up in the "Collaborative Paris-Centre Obesity Clinic" (Pitié-Salpêtrière Hospital: C. Poitou and JM. Oppert). In total, data from 4 additional unpublished cases were included in this report.

Study characteristics

Systematic review led to the identification of case reports or case series only. Cases were from Germany (24, 26, 29), Canada (25), USA (12, 27), France (28), and Switzerland (30). Among these 8 studies, we identified 17 cases. Adding the 4 unpublished cases, we included a total of 21. These cases were characterized by the following procedure types: 6 cases were treated with LAGB, 8 with SG, 6 with RYGB and 1 with BPD.

Phenotype before craniopharyngioma and before bariatric surgery

Mean age at the time of craniopharyngioma surgery was 16 y and mean BMI was 23.5 kg/m2. Before bariatric surgery, mean age was 24 y and mean BMI was 49.6 kg/m2. The mean BMI prior to bariatric surgery was 55.2 kg/m2 for the RYGB group, 48.9 kg/m2 for the SG group and 45.6 kg/m2 for the LAGB group. Note there was only one case for BPD. Before bariatric surgery, 6 among 17 patients with data were known to be diabetic (antidiabetic drug use and/or fasting blood glucose > 7 mmol/) and only one patient among 18 was treated for hypertension. (Table 1)

Absolute weight loss (kg) at 6 and 12 mo after bariatric surgery

Compared to baseline, mean weight change at 6 mo was –20.9 kg [95% CI: –35.4, –6.3] and at 12 mo was –15.1 kg [-31.7, +1.4]. Mean weight loss was greater in the

Table 1. Population characteristics

Patient	Bariatric procedure	Gender	Craniopharyngioma surgery Age, y	Diabetic status at bariatric surgery BMI, kg/m^2	Hypertension at bariatric surgery	Age at bariatric surgery	BMI before surgery and during follow-up, kg/m^2			
								Before	6 months	12 months
1	LAGB	F	9	-	0	0	17	44.8	42.7	43.3
2	LAGB	F	2	17.3	0	0	14	45.3	39.2	44.8
3	LAGB	M	13	27.4	0	0	17	43.8		44.6
4	LAGB	F	12	26.9	0	0	21	52.1	45.1	42.5
5	LAGB	F	44	30	1	0	54	47.1	42.1	42.8
6	LAGB	F	20	21.6	1	0	24	40.2	36.2	
7	RYGB	F	6	17.1	0	0	12.7	65.1	52.6	56
8	RYGB	M	8	-	1	0	29	48.5	35.1	31.3
9	RYGB	M	15	25	0	0	18.5	67	55.1	56.7
10	RYGB	F	16.5	21			25	51.6	37.6	39
11	RYGB	F	10	-	0	0	16	61.6	47.1	41.5
12	RYGB	F	29	23	1	0	30.5	37.5	38.8	38
13	SG	F	7	22	0	0	12	55	48.7	
14	SG	M	12	27	0	0	24	51	41.5	39.5
15	SG	M	39	31.5	1	0	43	37.6	33.6	31.7
16	SG	F	15	18.7	1	0	20	55.9	40.9	46.7
17	SG	F	7	22			12	57.9	47	49
18	SG	F	27	26	0	0	42	35.5	24.9	21.8
19	SG	F	5	18	0	0	20	55.4	39.8	50.5
20	SG	M	30	28.9	0	1	45	43.6	35.9	
21	BPD	M	4	19.4	0	0	15	45	40.4	34

LAGB: Laparoscopic adjustable gastric banding. RYGB: Roux en Y gastric bypass. SG: Sleeve gastrectomy. BPD: Biliopancreatic diversion.

RYGB group: –31.0 [-77.5, +15.5] kg at 6 mo and –33.7 [-80.7, +13.3] kg at 12 mo. In the SG group, values were: –28.3 [-51.3, –5.3] kg at 6 mo and –25.9 kg [-59.7, +7.9] kg at 12 mo. Finally, in the LAGB group weight loss was: –12.9 [-33.5, +7.7] kg at 6 mo and –7.5 [-28.2, 13.2] kg at 12 mo (Figure 3).

Relative weight loss (%) at 6 and 12 mo after bariatric surgery

Relative weight change was maximal at 6 mo for the LABG and SG groups, whereas it was maximal at 12 mo for the RYGB group and for the only case of BPD. After 6 mo, weight had decreased by 10.5% in the LAGB group, by 20.7% in the SG group, by 18.6% in the RYGB group, and by 11.3% for the BPD patient. After 12 mo, net weight loss from baseline was 6.1% in the LAGB group, 19.6% in the SG group, 20.2% in the RYGB group, and 24.8% for the BPD patient.

At one year, among 18 cases with follow-up data, 6 had lost more than 20% of their initial weight; all had undergone either RYGB (n = 3), SG (n = 2) or BPD (n = 1). All patients who had lost less than 5% of their initial weight had undergone LAGB except one RYGB case.

Follow-up data for more than one year after bariatric surgery were available for only 15 individuals, at different time points. Each patient's data is presented in the Webtable 2.

Diabetic status after bariatric surgery

The percentage of diabetic patients had decreased from 31.6% to 7.1% at 6 mo and to 8.3% at 12 mo (Webtable 3).

Discussion

This study is the first systematic review with meta-analysis, including the largest number of cases with craniopharyngioma who underwent a bariatric surgery, with prospective follow-up at 6 and 12 mo. In addition to the literature search, we were able to include data from 4 unpublished patients which represents almost 25% cases in this review. This reflects the difficulties to reach reliable data quality in orphan diseases in general, but, vice versa, also demonstrates the urgent need for systematic investigations to improve treatment strategies in this condition. Our meta-analysis suggests that the expected level of weight loss was significant at 6 and at 12 mo. RYGB was the most effective weight loss strategy, followed by the SG and LAGB; weight rebound at 12 mo was seen for patients treated by SG and LAGB.

Bariatric surgery leads to weight loss by mechanisms that are still poorly understood, and which likely vary by procedure. Proposed mechanisms by which procedures induce weight change include alteration of physiologic

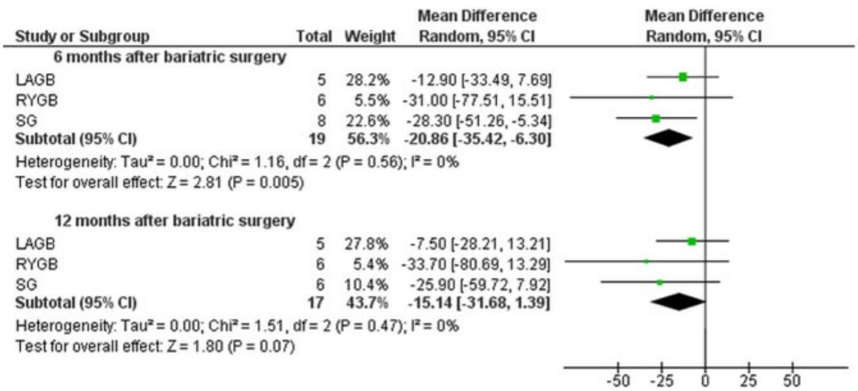

Figure 3. Mean differences in weight at 6 mo and 12 mo after bariatric surgery across surgical procedures. *LAGB: Laparoscopic adjustable gastric banding. RYGB: Roux en Y gastric bypass. SG: Sleeve gastrectomy.Weight in kilograms. Biliopancreatic diversion was excluded because only 1 patient underwent this bariatric surgical procedure.*

mechanisms of afferent signaling of satiety and appetite (RYGP, SG, and BPD), mechanical restriction/obstruction (LAGB), and intestinal malabsorption (BPD, RYGB). In exogenous obesity, weight loss is excellent, greater after RYGB than with most other commonly used procedures (15). Our study confirms this for HyOb due to craniopharyngioma. Gastrointestinal hormonal changes that are seen following RYGB, SG and BPD (e.g., increase of GLP-1 or PYY levels and a decrease in orexigenic hormones such as ghrelin), may in part be responsible for the difference in weight loss efficacy as compared to purely restrictive procedures (31, 32). Several investigations indicated that one of the major risk factors for obesity after childhood craniopharyngioma treatment is hypothalamic tumor involvement (5, 33). In our meta-analysis the significantly greater weight loss observed after RYGB, compared to other procedures, might indicate that CNS targets for mediators of satiety/appetite affected by RYGB are not completely disrupted by the craniopharyngioma treatment. In this regard, it is known that receptors for ghrelin, an orexigenic gut hormone that is believed important for appetite, are found in various regions including the brainstem and midbrain (34, 35) which would not predictably be damaged by treatment of a tumor located in the sellar or parasellar region. In recent publications, the use of functional MRI has also highlighted the potential role of the orbitofrontal cortex, the insula and the striatum as targets for both orexigenic and anorexigenic signals from the periphery (36). Indeed, combined administration of PYY and GLP-1 lead to a reduction in MRI signal in theses areas (37).

Another interesting observation from this examination of the published literature is that some surgeons during the course of a bariatric procedure also included truncal vagotomy, presumably in an effort to attenuate the vagal contribution to hyperinsulinemia. In one case treated with RYGB, the procedure was combined with anterior truncal vagotomy which may have affected the outcome (27). The role of vagotomy in obesity treatment was first examined by Kral et al. in 1978 showing important weight loss among 3 women after vagotomy without serious side-effects (38). However, most do not believe that there is an additional weight loss effect of vagotomy when combined with modern bariatric procedures, as shown with LAGB in a recent trial (39). Furthermore, there are only two cases reporting vagotomy in craniopharyngioma patients, both combined with a RYGB (27, 40). These cases achieved approximately the same percentage of weight loss compared to patients without additional vagotomy.

In patients with exogenous obesity, several studies have shown that weight loss was maximal one year after bariatric surgery regardless of the procedure performed (15, 19). Our meta-analysis focused on HyOb following treatment of craniopharyngioma, and found that bariatric procedures were not as effective for weight reduction as reported for adults with exogenous obesity. In the SOS study, the mean percentage of weight loss at one year was 37% in the bypass group and approximately 20% in the banding group (15). Regarding SG, no weight rebound was noted between 6 and 12 mo in a recent report of 1,000 cases (41).

HyOb after craniopharyngioma treatment mainly affects adolescents and young adults. In our meta-analysis, 8/21 cases were adolescents and 6/21 were younger than 25 y at the time of bariatric surgery. Little is known about long-term outcomes in adolescents treated with bariatric surgery as yet only few studies are available (42, 43, 44). Two years after LAGB, O'Brien et al. have shown a mean weight loss of 34.6 kg in 25 adolescents which represents 23.8% of variation in weight (45). Holterman and colleagues reported that 18 mo after LAGB morbidly obese (BMI $<$ 50 kg/m2) and superobese (BMI [mteq] 50 kg/m2) adolescents had an equivalent mean weight loss of 28 kg and 30 kg respectively (43). Examination of trends in laparoscopic bariatric surgery in adolescent with exogenous obesity reveals an increased use of SG, in line with a decreased use of LAGB while the frequency of RYGB remains stable (46). Unlike the guidelines for bariatric surgery in adults which are well established (47, 48), those for adolescents are still being debated (49, 50). In 2008, the Endocrine Society published a Clinical Practice Guideline on the prevention and treatment of pediatric obesity and recommended limiting bariatric surgery to adolescents with a BMI [mteq] 50 or [mteq] 40 kg/m2 with significant severe comorbidities (51). In 2009, the *International Pediatric Endosurgery Group* also published guidelines with the same BMI cut-offs for surgery in adolescents as in adults: a BMI [mteq] 40 kg/m2 or a BMI [mteq] 35 kg/m2 with comorbid disease (52). Theses two guidelines included similar additional criteria such as a Tanner [mteq] 4 development stage, near-final adult height or 95% skeletal maturity, a demonstrated commitment to lifestyle change and a stable psychosocial environment. Authors also stressed the importance of the surgeon's experience and as well as the capability of the patient to fully understand the surgical procedure with its consequences, particularly in term of nutrition after malabsorptive procedures like RYGB. Theses guidelines also highlighted the importance of intensive multidisciplinary preoperative evaluation including a psychological approach, especially for adolescents.

Appropriate timing of bariatric surgery in adolescents with HyOb following treatment of craniopharyngioma is an important issue that needs to be further considered. Recently, a retrospective analysis indicated that most of the weight gained was observed in the first year after diagnosis or surgery of craniopharyngioma (7). It is increasingly appreciated that the efficacy of RYGB surgery for weight reduction obeys a "ceiling" of approximately 30%–35% acute weight loss in most cases of exogenous obesity (53). Thus, if one can predict maximal weight induced by surgery, then shouldn't this information be considered in medical decision-making when one is tracking and documenting massive weight gain following treatments known to disrupt energy balance mechanisms? Early and safe application of bariatric procedures designed to decelerate or stabilize this well known weight gain phenotype after hypothalamic surgery could potentially mitigate development of long-term obesity related health problems in these cases. While some have suggested that LAGB or SG could be a first therapeutic option before RYGB later in adulthood (24), there is little evidence upon which to base a staged bariatric treatment recommendation at this time.

It is also apparent that those undergoing craniopharyngioma surgery need a high level of compliance with daily treatment for pituitary insufficiency and supplementation to prevent vitamin deficiencies. The malabsorption induced by RYGB and even more by BPD poses the dilemma of whether appropriate absorption of medications and hormonal replacement for pituitary deficiencies is to be expected. However, these concerns about malabsorption of needed replacement endocrine therapy after RYGB have not yet been well studied. Schutles et al. have shown that 18 mo after a RYGB and a weight loss of 50 kg, hydrocortisone dosing could be reduced to 10–15 mg per day, desmopressin dosing was reduced by 6-fold and the growth hormone (GH) dosing was increased by 6-fold (30). There will likely be some variation in absorption after surgery according to drug characteristics, bioavailability, routes of administration, doses and surgery types. It also reveals the lack of knowledge in the field of pharmacology in bariatric surgery. In a recent systematic review, evidence for diminished drug absorption was found in 15/22 studies involving jejunoileal bypass, a third of the studies of RYGB and none for BPD (54).

In HyOb the operative and postoperative risks are more important. Patients are often morbidly obese with severe comorbidities and complete pituitary deficiencies. In the studies included in this review, few authors described the postoperative outcomes, including reoperation, vitamins deficiency, and hypoglycemia. Restrictive procedures for HyOb may be more safe due to the shorter length of time for anesthetic, procedure and recovery and may pose a lower risk for vitamin and mineral deficiencies (24, 26). However, these procedures also seem to be less effective than RYGB and SG.

The limitations of this study include the nature of the data (only case reports or series), the lack of standardized evaluation of the preoperative food craving and hyperphagia, differences in surgery procedures and the small sample size. Nonetheless, the value of collective analysis of rare cases cannot be underestimated, as it permits important comparisons and considerations of knowledge gaps in the field. In rare diseases it may be very difficult to perform adequate clinical trials and meta-analysis may help to resolve this problem (55, 56). In addition, as the overwhelming majority of published experience in this area is retrospective, it is likely that there is a publication bias in the literature, which may predictably result in a higher likelihood of good outcomes of surgery being published. This type of bias could be mitigated by the availability of a registry by which patients could agree to participate in prospective studies and self-report outcomes of interventions for weight loss. The International Registry for Hypothalamic Obesity Disorders (www.irhod.org) is such a registry and in the future may be useful for planning of studies that include larger numbers of subjects than are possible in any single center currently.

In conclusion, this systematic review and meta-analysis indicates that bariatric surgery induces important weight loss at one year, in obese patients following treatment of craniopharyngioma, even if the impact seems less important than for common obese patients. There are no current guidelines for bariatric surgery in patients with lesional HyOb. Well designed prospective studies, with appropriate follow-up, are needed to clarify the role of specific bariatric procedures in HyOb due to craniopharyngioma.

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Supplemental Files:

Table 1. Research strategies in MEDLINE and EMBASE databases

Table 2. Long-term body mass index relative change after bariatric surgery

in different time intervals*

*Time in months are indicated in bracket. * Relative change is defined as: (follow BMI – initial BMI)/initial BMI * 100*

Figure 1. Diabetic status after bariatric surgery (diabetic patients/patients with available data)

Diabetic status is defined as follows: anti-diabetic drug use and/or fasting blood glucose >7mmol/

Webtable 1. Research strategies in MEDLINE and EMBASE databases.

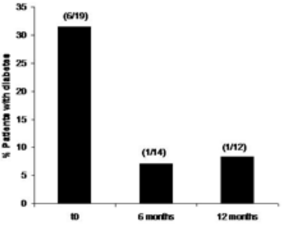
<u>MEDLINE (10 results).</u> **#1** “obesity” [MESH]:: 163958 results. **#2** “craniopharyngioma” [MESH]:: 4040 results. **#3** “gastric surgery”: 110414 results. **#4** “bariatric surgery” [MESH]:: 13596 results. **#5** #1 AND #2 : 163 results **#6** #3 AND #5 : 7 results **#7** #4 AND #5 : 9 results **#8** #6 OR #7 : 10 results
<u>EMBASE (21 results).</u> **#1** “obesity” [EMTREE]: 268020 results. **#2** “craniopharyngioma” [EMTREE]: 5134 results. **#3** “gastric surgery” [EMTREE]: 67201 results. **#4** “bariatric surgery” [EMTREE]: 13892 results. **#5** #1 AND #2 : 281 results **#6** #3 AND #5 : 9 results **#7** #4 AND #5 : 19 results **#8** #6 OR #7 : 21 results

Webtable 2. Long-term body mass index relative change after bariatric surgery in different time intervals*

Patient's ID	1 year	1-2 years	2-5 years	5 years and more
1	-3.3			
2	-1.1	-15.2 (24 months)		
3	1.8	2.9 (24 months)	14.8 (36 months)	
4	-18.4	-11.9 (24 months)	0.2 (36 months)	
5	-9.1			-4.7 (60 months)
6		-2.7 (24 months)	3.2 (42 months)	-0.7 (60 months)
7	-14.0			-34.0 (60 months)
8	-35.4	-34.2 (18 months)		
9	-15.4		-22.1 (30 months)	-20.7 (75 months)
10	-23.5			
11	-32.6	-28.1 (24 months)		
12	1.3			30.7 (64 months)
13	-15.6			
14	-22.5		-19.6 (41 months)	
15	-15.7		-9.6 (30 months)	
16	-16.4	3.4 (24 months)		
19	-8.8		-11.7 (36 months)	
21	-24.4	-28.9 (24 months)		

Time in months are indicated in bracket.

* *Relative change*



35
30
25
20
15
10
5
0
% Patients with diabetes
(6/19)
(1/14)
(1/12)
t0
6 months
12 months

		LABG				RYGB				VSG			
		mo	BMI	mo	BMI	mo	BMI	mo	BMI	mo	BMI	mo	BMI
1		12	-3.3										
2		12	-1.1	24	-15.2								
3		12	1.8	36	14.8								
4		12	-18.4	36	0.2								
5		12	-9.1	60	-4.7								
6				24	-2.7								
7						12	-14	60	-34				
8						12	-34.5	18	-34.2				
9						12	-15.4	75	-21				
10						12	23.5						
11						12	-32.6	24	-28.1				
12						12	1.3	64	30.7				
13										12	-15.6		
14										12	-22.5	41	-19.6
15										12	-15.7	30	-9.6
16										12	-16.4	24	3.4
17													
18													
19										12	-8.8	36	-11.7
20													
21													
mean		12	-6.02	36	-1.52	12	-11.95	48.2	-17.32	12	-15.8	32.75	-9.375
median		12	-3.3	36	-2.7	12	-14.7	60	-28.1	12	-15.7	33	-10.65