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Bariatric Surgery for Hypothalamic Obesity in Craniopharyngioma Patients: A Retrospective, Matched Case-Control Study

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Abbreviations: ANOVA, analysis of variance; BMI, body mass index; DDAVP, 1-desamino-8-D-arginine vasopressin; GLP-1, glucagon-like peptide 1; IGF-1, insulin-like growth factor 1; LAGB, laparoscopic gastric banding; SDS, Standardized Deviation Scores; SOReg, Scandinavian Obesity Surgery Registry.

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Abstract

Context: Craniopharyngioma is a sellar tumor associated with high rates of pituitary deficiencies (~ 98%) and hypothalamic obesity (~ 50%).

Objective: This work aims to determine the efficacy regarding long-term weight loss after bariatric surgery in obese craniopharyngioma patients with hypothalamic dysfunction.

Methods: This retrospective, case-control, multicenter, international study included obese craniopharyngioma patients ($N = 16$; of whom 12 are women) with a history of bariatric surgery

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(12 Roux-en-Y gastric bypass, 4 sleeve gastrectomy; median age 21 years [range, 15-52 years], median follow-up 5.2 years [range, 2.0-11.3 years]) and age/sex/surgery/body mass index–matched obese controls ($N = 155$). Weight loss and obesity-related comorbidities up to 5 years after bariatric surgery were compared and changes in hormonal replacement therapy evaluated.
Results: Mean weight loss at 5-year follow-up was 22.0% (95% CI, 16.1%-27.8%) in patients vs 29.5% (95% CI, 28.0%-30.9%) in controls ($P = .02$), which was less after Roux-en-Y gastric bypass (22.7% [16.9%-28.5%] vs 32.0% [30.4%-33.6%]; $P = .003$) but at a similar level after sleeve gastrectomy (21.7% [–1.8% to 45.2%] vs 21.8% [18.2%-25.5%]; $P = .96$). No major changes in endocrine replacement therapy were observed after surgery. One patient died (unknown cause). One patient had long-term absorptive problems.
Conclusion: Obese patients with craniopharyngioma had a substantial mean weight loss of 22% at 5-year follow-up after bariatric surgery, independent of type of bariatric surgery procedure. Weight loss was lower than in obese controls after Roux-en-Y gastric bypass. Bariatric surgery appears to be effective and relatively safe in the treatment of obese craniopharyngioma patients.

Key Words: craniopharyngioma, hypothalamic obesity, hypothalamic dysfunction, bariatric surgery, weight loss, case-control study

Craniopharyngiomas are rare brain tumors that mostly affect children or older adults (1-3). They are typically located in the sellar and suprasellar regions (1, 2). State-of-the-art treatment for craniopharyngiomas is tumor resection with or without radiotherapy (2). Although craniopharyngiomas usually have a benign histology, treated patients often suffer from severe long-term sequelae as a result of hypothalamic dysfunction due to tumor localization or therapeutic interventions (2-4).

In addition to the necessity for life-long hormone replacement therapy due to hypopituitarism, hypothalamic dysfunction can also cause eating disorders such as hyperphagia, leading to obesity in 50% to 75% of the patients (2, 5, 6). Energy expenditure may also be decreased and cognitive performance can be weak, which can interfere with conservative weight-loss strategies (2, 7). Morbid hypothalamic obesity and associated complications like type 2 diabetes, hypertension, obstructive sleep apnea syndrome, hypersomnia, and increased daytime sleepiness have a major impact on quality of life in patients with craniopharyngioma (3, 6, 8-11). The morbid obesity and related comorbidities contribute to an increased cardiovascular mortality (3, 6, 8-11).

Because pharmacologic treatment options are limited (12), bariatric surgery might be a promising treatment strategy in combating obesity in patients with craniopharyngioma. Key to the effectiveness of bariatric surgery in the general obese population is a decrease in appetite, which is caused by changes in gastrointestinal hormones such as glucagon-like peptide 1 (GLP-1) (13, 14). GLP-1 activates neurons in the hypothalamus that influence satiety, feeding, the sympathetic nervous system, and the pituitary (12, 13). Bariatric surgical procedures are not all equally effective—gastric bypass surgery seems to be the most promising option in the general population (15-17). However, the question remains whether bariatric surgery is still effective if the hypothalamus is damaged, as is often the case in patients with craniopharyngioma (2). Previously, studies that were hampered by a follow-up of 2 years or less reported a significant weight reduction following gastric bypass surgery in patients with severe hypothalamic obesity without postoperative impairment of oral hormone replacement therapy for pituitary insufficiencies (16-18).

In patients suffering from morbid obesity in the general population, bariatric surgery is an efficient treatment with sustained long-term weight loss (19, 20). However, data on the long-term effects of bariatric surgery in morbid hypothalamic obesity due to a craniopharyngioma are limited. This is a major barrier in providing evidence-based advice to patients. This study therefore aimed at analyzing (medium) long-term weight reduction following gastric bypass and sleeve gastrectomy surgery in obese craniopharyngioma patients compared to a matched control group from a general obese population treated with bariatric surgery, and at describing safety aspects regarding pituitary hormone replacement therapy.

Materials and Methods

Study Design and Participants

In this international, multicenter, matched case-control study, patients with a history of craniopharyngioma and bariatric surgery to treat hypothalamic obesity were compared to bariatric surgery patients from a general obese

population. Sixteen patients with histopathology-proven craniopharyngioma with 2 years or longer follow-up were included from the Erasmus Medical Center, Rotterdam, the Netherlands (n = 4) (17), the Sahlgrenska University Hospital, Gothenburg, Sweden (n = 4) (17), the Medical University Hospital of Vienna, Austria (n = 5), University Hospital Erlangen, Erlangen, Germany (n = 2), and the Federal University of Parana, Curitiba, Brazil (n = 1). The study methods and the Dutch/Swedish patients have been previously described (17); this report increased patient numbers by recruiting from additional centers and increased the follow-up duration. This international study followed all national laws and recommendations in the country where the patient was treated concerning ethical approval and written consent. The study was approved by all local ethics committees. Two patients underwent a second bariatric surgery procedure: One had the Roux-en-Y gastric bypass approximately 20 months after a sleeve gastrectomy because of insufficient weight loss and abdominal pain, and 1 patient had a Roux-en-Y gastric bypass approximately 6 years after gastric banding (the gastric banding was removed after 1 week because of abdominal complaints). Data from the second bariatric surgery onward were applied in this analysis. Hypothalamic damage was defined as injury to the hypothalamus and/or third ventricle, diagnosed by neuroimaging and/or neurosurgery reports (8). Patients with a history of radiotherapy were considered at high risk of hypothalamic dysfunction and therefore also included in the study if they met all other inclusion criteria.

Matching Procedure for Controls

Controls were acquired from the Scandinavian Obesity Surgery Registry (SOReg), a Swedish nationwide registry. The patients were matched to controls from a sample of 69 672 individuals who were preselected from the total cohort of 75 600 SOReg participants after exclusion of individuals who were not Swedish, were reoperated on, had surgery before 2007, or had a procedure other than gastric bypass surgery or sleeve gastrectomy. Controls had follow-up data on body weight (in kilograms) available at 6 weeks, and at 1, 2, and 5 years after bariatric surgery. Patients had considerable variation in follow-up duration because of the retrospective design. Missing data for 3- and 4-year follow-up in controls and 1- to 5-year follow-up in patients were interpolated linearly between the 2 closest available time points. The matching procedure was extensive: potential controls were first selected according to sex, type of bariatric surgery (Roux-en-Y gastric bypass or sleeve gastrectomy), preoperative type 2 diabetes, and preoperative hypertension. Further matching was performed by year of obesity operation (10-year span category), age at obesity operation (10-year span category), and preoperative body mass index (BMI) (maximum of ± 5 different from the control). Controls were included only once. If fewer than 10 controls were found, the criteria for matching age at bariatric surgery were extended to ± 10 years of the patient's age instead of a certain age category, which was required in 5 patients. For one patient, the criteria for BMI were extended as this patient was an outlier because of an extremely high BMI: the best-matched controls were chosen without a limit to BMI criteria. Ultimately, all patients were each matched with 10 controls except for 2 patients: nine controls were found for 1 and 6 controls were found for the extreme outlier. This resulted in the selection of 155 optimally matched controls (mean BMI difference –1.1; maximum BMI difference between patient and control, 0.04-12.6).

Outcomes of Interest

Data were gathered retrospectively. Outcomes of interest were percentage weight change at 6 weeks, at 1, 2, 3, 4, and 5 years, and at last available follow-up after bariatric surgery. The presence of type 2 diabetes, hypertension, and dyslipidemia as comorbidities before bariatric surgery and during follow-up, and complications of the bariatric procedure were evaluated. We studied alterations in hormone replacement therapy for pituitary deficiency in patients with craniopharyngioma (17). For insulin-like growth factor 1 (IGF-1) values, SD scores (SDS) were calculated if the applied assay and normative data were known (21-24).

Statistical Procedure

Statistical analysis was performed using the Statistical Package for Social Sciences (IBM SPSS Statistics 25). Continuous data are represented as mean ± SD, or median and range; categorical data are represented as frequencies and percentages. Baseline statistics were compared between patients with obesity after craniopharyngioma and the matched controls from the SOReg database by Mann-Whitney *U* test and Fisher exact test for continuous and categorical data, respectively. Related continuous data were evaluated with the Wilcoxon rank test. A 2-way analysis of variance (ANOVA) was used to compare percentage weight change between patients and controls. In this procedure, a one-factor generalized randomized block design was applied with matched case-control units included as blocks. Percentage weight change was applied as the dependent variable and type of participant (patient with craniopharyngioma or control) as the independent variable in the 2-way ANOVA.

Bootstrapping with 1000 replicates was performed to meet the normality assumption related to the 2-way ANOVA test (17).

Results

Patient Characteristics

The characteristics of the 16 craniopharyngioma patients treated with bariatric surgery are shown in Table 1. Twelve (75%) patients were female and 13 (81%) had childhood (age < 18 years) onset of disease. Initial treatment for craniopharyngioma was surgery (n = 13 [81%]), surgery and radiotherapy (n = 2 [13%]), and cyst aspiration (n = 1 [6%]). Two patients (13%) had a history of recurrence of craniopharyngioma twice, and 9 patients (56%) had residual tumor tissue on their last magnetic resonance imaging scan. All patients had signs of either hypothalamic damage or third-ventricle involvement on magnetic resonance imaging (n = 13 [87%, data missing for one patient]), or a history of radiotherapy (n = 7 [44%]). Two patients (13%) had used medication to treat obesity before bariatric surgery: sibutramine with no results, and sibutramine and orlistat with no results and no results/side effects, respectively. Twelve patients (75%) underwent Roux-en-Y gastric bypass, and 4 patients (25%) underwent sleeve gastrectomy. Median follow-up duration of the patients since bariatric surgery was 5.8 years (range, 2.0-11.3 years), hereafter being referred to as last follow-up.

A comparison of baseline characteristics of patients with craniopharyngioma and their controls with "common" obesity matched for age, sex, comorbidity, BMI, and bariatric surgery is shown in Table 2. Baseline characteristics were comparable between patients and controls except for age at bariatric surgery (with a slightly lower mean age of 26 years [SD 12] in patients vs 31 years [12] in controls; $P = .03$) and more frequent presence of dyslipidemia before surgery (4/16 [25%] in patients vs 6/155 [4%] in controls; $P = .008$); the difference in the presence of dyslipidemia between patients and controls before surgery was more pronounced in those undergoing sleeve gastrectomy (3/4 [75%] vs 1/39 [3%]; $P = .001$]. The occurrence of dyslipidemia before bariatric surgery was higher in craniopharyngioma patients who had a gastric sleeve than in those who underwent gastric bypass (3/4 [75%] vs 1/12 [8%]; $P = .03$).

Weight Change After Bariatric Surgery

Mean weight loss at 5 years after surgery was 22.0% (95% CI, 16.1%-27.8%) in craniopharyngioma patients compared to 29.5% (95% CI, 28.0%-30.9%) in controls ($P = .02$; Table 3 and Fig. 1). Patients had significantly less weight loss compared to controls from 1- to 5-year follow-up after any bariatric surgery procedure and from 2- to 5-year follow-up after Roux-en-Y gastric bypass specifically, but not after sleeve gastrectomy specifically. Mean weight loss at 5-year follow-up after Roux-en-Y surgery was less in patients compared to controls (22.7% [95% CI, 16.9%-28.5%] vs 32.0% [95% CI, 30.4%-33.6%]; $P = .003$) but was comparable at 5-year follow-up after sleeve gastrectomy comparing patients and controls, respectively (21.7% [95% CI, –1.8% to 45.2%] vs 21.8% [95% CI, 18.2%-25.5%], $P = .96$). If the type of bariatric surgery is compared in patients or controls as a group, mean percentage weight loss at 4-year follow-up in controls was higher after Roux-en-Y gastric bypass compared to sleeve gastrectomy (33.0 [SD 7.8] vs 24.0 [9.9]; $P < .001$), but not different when comparing these bariatric procedures in craniopharyngioma patients (21.8 [12.0] vs 19.1 [5.7], $P = 1.00$). Fig. 2 shows the percentage of patients and controls in 5% weight loss categories at 2- and 4-year follow-up. At last follow-up, 8 (50%) of 16 patients had lost at least 20% of their original body weight, 3 (19%) between 10% and 15%, 3 (19%) between 5% and 10%, and 1 (6%) had less than a 5% weight loss, while 1 (6%) showed weight increase. Among the patients who used sibutramine, one had at least 20% weight reduction and the other had 5% to 10% weight loss at last follow-up. There was no significant difference in mean percentage weight loss at last follow-up comparing patients with (n = 13) and without (n = 2) hypothalamic damage or third-ventricle involvement (23.2% [SD 16.6] vs 10.5% [5.4]; $P = .23$, one missing) and those with (n = 7) and without (n = 9) radiotherapy (16.6% [16.9] vs 23.5% [15.7]; $P = .41$), respectively.

Cardiometabolic Features

The prevalence of type 2 diabetes before bariatric surgery was similar in patients and controls (1/16 [6%] vs 10/155 [6%]; $P = 1.00$). At last follow-up, type 2 diabetes had resolved in all participants except for one control, resulting in similar percentages in patients and controls (0/16 [0%] vs 1/155 [1%]; $P = 1.00$). Dyslipidemia occurred more often in patients than controls before bariatric surgery (4/16 [25%] vs 6/155 [4%]; $P = .008$) and at last follow-up (2/15 [13%; one missing data] vs 2/155 [1%]; $P = .04$). Hypertension occurred at a similar prevalence in patients and controls before bariatric surgery (4/16 [25%] vs 35/155 [23%]; $P = .76$) and there was no significant difference at last follow-up (0/16 [0%] vs 18/155 [12%]; $P = .22$), although all cases of hypertension in patients were resolved at last follow-up.

Table 1. Baseline demographic and clinical characteristics of patients with craniopharyngioma

Characteristic	Craniopharyngioma patients (N = 16)
Sex, No. (%)	
Women	12 (75)
Men	4 (25)
Median (range) age at first craniopharyngioma treatment, y	12 (4-48)
Median age (range) at last follow-up, y	33 (17-61)
Mean (SD) follow-up duration since craniopharyngioma surgery at last follow-up, y	11.9 ± 3.8
Treatment for craniopharyngioma, No. (%)	
Surgery	
Initially[a]	15 (94)
Ever	15 (94)
Median (range) No. of craniopharyngioma surgeries	1 (1-6)
Radiotherapy	
Initially, in addition to surgery	2 (13)
Ever	7 (44)
Mean (SD) cumulative radiotherapy dose, mGy	4225 ± 1801
Hypothalamic damage, No. (%)	9 (60)
Third-ventricle involvement, No. (%)	9 (60)
Hypothalamic damage and/or third-ventricle involvement, No. (%)	13 (87)
Hypothalamic damage and/or third-ventricle involvement and/or radiotherapy, No. (%)	16 (100)
Pituitary deficiencies	
GH deficiency	
Frequency, No. (%)	16 (100)
Median (range) age at occurrence, y	13 (6-49)
GH replacement therapy at last follow-up, No. (%)	14 (88)
TSH deficiency	
Frequency, No. (%)	15 (94)
Median (range) age at occurrence, y	14 (4-48)
Gonadal axis deficiency	
Frequency, No. (%)	14 (88)
Median (range) age at occurrence, y	13 (6-48)
Gonadal replacement therapy at last follow-up, No. (%)	12 (75)
ACTH deficiency	
Frequency, No. (%)	12 (75)
Median (range) age at occurrence, y	12 (4-48)
ADH deficiency	
Frequency, No. (%)	14 (88)
Median (range) age at occurrence, y	12 (4-48)
Use of antiepileptic drugs, No. (%)	2 (13)
Bariatric procedure	
Median (range) age at bariatric surgery, y	21 (15-52)
Mean (SD) BMI before bariatric surgery	46.0 ± 8.0
Median (range) follow-up since bariatric procedure, y	5.8 (2.0-11.3)

Abbreviations: ACTH, adrenocorticotropin; ADH, antidiuretic hormone; BMI, body mass index; GH, growth hormone; TSH, thyrotropin.
[a]Excluding one patient treated with cyst aspiration initially.

Complications After Bariatric Surgery

Five patients experienced short-term perioperative and postoperative complaints or issues: postoperative abdominal pain (n = 1), dumping syndrome (n = 1), inability to eat solid food because of abdominal fullness (n = 1), stenosis of the anastomosis (n = 1), a generally complicated postoperative course with nephrolithiasis, pulmonary embolism, and postinfarction pneumonia (n = 1). Regarding long-term complications, one patient suffered from long-term severe absorptive problems ever since the bariatric surgery, which was accompanied by malnutrition and a low quality of life. One patient died at age 32 years, approximately 2.5 years after their second bariatric surgery; the cause of death was unknown. Because the cause

Table 2. Baseline characteristics of patients treated with bariatric surgery: craniopharyngioma-related hypothalamic obesity vs controls with "common" obesity

Characteristic	Craniopharyngioma patients (N = 16)	Matched controls (N = 155)
Sex, No. (%)		
Female	12 (75)	119 (77)
Male	4 (25)	36 (23)
Mean (SD) age at bariatric surgery, y	26.4 ± 12.1	30.5 ± 11.5[a]
Bariatric procedure, No. (%)		
Roux-en-Y gastric bypass	12 (75)	116 (75)
Sleeve gastrectomy	4 (25%)	39 (25)
Mean (SD) preoperative BMI	46.0 ± 8.0	45.1 ± 6.9
Roux-en-Y gastric bypass	45.4 ± 6.0	44.9 ± 5.6
Sleeve gastrectomy	48.0 ± 13.5	45.6 ± 9.7
Preoperative diabetes mellitus, No. (%)	1 (6)	10 (6)
Preoperative hypertension, No. (%)	4 (25)	35 (23)
Preoperative dyslipidemia, No. (%)	4 (25)	6 (4)[b]

Abbreviation: BMI, body mass index.
[a]*P* equals .03.
[b]*P* equals .008.

of death could not be determined, an adrenal insufficiency cannot be excluded as a contributing factor to the fatality.

Replacement Therapies for Pituitary Deficiencies

Fifteen (95%) of the 16 patients needed minor-to-moderate changes of pituitary hormone replacement therapy during follow-up, the only exception being a patient receiving only growth hormone replacement therapy (see Table 1 for baseline pituitary deficiencies, and Figs. 3 and 4 for individual changes of replacement therapy). All patients were growth hormone deficient. Mean daily growth hormone dose was not significantly different before bariatric surgery vs last follow-up (0.92 [SD 0.65] vs 0.72 [0.88] mg; $P = .50$); similarly, mean IGF-1 (19.4 [10.1] vs 34.0 [57.6] nmol/L; $P = .72$) and mean IGF-1 SDS values (–1.6 [1.6] vs –0.7 [2.0]; $P = .61$) did not change significantly (see Fig. 3). One patient did not initially receive growth hormone replacement therapy because of fear of tumor growth, but the patient reconsidered and decided to start during follow-up. Three patients stopped using growth hormone replacement therapy at some point during follow-up, one because of a diagnosis of a malignancy (see Fig. 3).

Fourteen (88%) of 16 patients had a gonadal hormone deficiency; 8 had no change in their replacement therapy and 1 did not use any during follow-up. Three patients switched type of gonadal hormone replacement therapy (estradiol/dydrogesterone to ethinylestradiol/levonorgestrel at different doses; multiple esters of testosterone every 15 days intramuscular to testosterone undecanoate every 3 months; and gel application to injection). One patient required only a minor dose change. One patient stopped treatment because of a liver adenoma.

Thyroid hormone replacement therapy was needed in 15 (94%) of 16 patients, of whom 5 had no changes in thyroid medication at all (see Fig. 4); mean daily levothyroxine dose was comparable before bariatric surgery and at last follow-up (199.5 [SD 59.8] vs 171.2 [40.6] µg; $P = .23$). Mean cumulative daily 1-desamino-8-D-arginine vasopressin (DDAVP) doses for central diabetes insipidus remained similar comparing before surgery to last follow-up (0.29 [0.29] vs 0.24 [0.10] mg; $P = .29$). DDAVP dose was unchanged in 10 patients (see Fig. 4). Mean cumulative daily hydrocortisone dose did not change from before bariatric surgery to last follow-up (25.5 [9.3] vs 24.2 [5.1] mg; $P = .85$).

Discussion

This is the first long-term case-control study on the outcome of bariatric surgery in the largest cohort of patients with craniopharyngioma and hypothalamic dysfunction to date. It showed a mean approximately 22% weight loss 5 years after bariatric surgery. All patients required minor adjustments of hormonal replacement therapy after bariatric surgery, which were anticipated as most patients underwent a serious change in body weight. Although these results are encouraging, weight loss was significantly less pronounced, but still clinically relevant, compared to obese controls without a history of craniopharyngioma.

This less dramatic weight loss for craniopharyngioma patients compared to controls was, however, observed only

Table 3. Percentage weight loss after bariatric surgery of patients with craniopharyngioma and matched controls

Time after surgery	% Weight loss (95% CI)							
	Sleeve gastrectomy			Roux-en-Y gastric bypass			Any bariatric surgery procedure		
	Patients	Controls	*P*	Patients	Controls	*P*	Patients	Controls	*P*
6 wk	18.1 (12.5 to 23.7)	14.7 (12.9 to 16.5)	.25	15.0 (12.1 to 18.0)	15.5 (14.6 to 16.4)	.74	15.8 (13.2 to 18.4)	15.3 (14.5 to 16.1)	.71
1 y	25.3 (17.4 to 33.2)	27.5 (25.0 to 30.0)	.60	28.7 (24.1 to 33.4)	33.5 (32.2 to 34.9)	.05	25.9 (22.1 to 29.7)	32.1 (30.8 to 33.3)	.003
2 y	23.8 (14.6 to 33.0)	27.1 (24.1 to 30.0)	.50	24.4 (19.2 to 29.6)	34.4 (32.7 to 36.1)	< .001	24.2 (19.7 to 28.7)	32.6 (31.1 to 34.0)	.001
3 y	28.9 (18.4 to 39.5)	25.5 (22.6 to 28.4)	.53	22.1 (16.9 to 27.3)	33.9 (32.2 to 35.5)	< .001	23.2 (18.5 to 27.9)	31.8 (30.4 to 33.2)	.001
4 y	22.5 (8.9 to 36.0)	24.0 (21.0 to 26.7)	.82	21.7 (16.8 to 26.7)	33.1 (31.5 to 34.6)	< .001	20.9 (16.2 to 25.6)	30.8 (29.4 to 32.2)	< .001
5 y	21.7 (–1.8 to 45.2)	21.8 (18.2 to 25.5)	.96	22.7 (16.9 to 28.5)	32.0 (30.4 to 33.6)	.003	22.0 (16.1 to 27.8)	29.5 (28.0 to 30.9)	.02

after Roux-en-Y gastric bypass. This is in contrast to the results of our previous study in a smaller cohort (17), when we found similar weight reduction after Roux-en-Y gastric bypass in patients with craniopharyngioma and controls, and less weight reduction in patients than controls after sleeve gastrectomy. The present study now includes the same Dutch and Swedish patients (17), but the sample size has been enlarged by international cooperation, leading to a larger cohort of patients with a considerably longer follow-up after the bariatric procedure. The number of patients who underwent sleeve gastrectomy is, however, still relatively small (n = 4).

In a comparative effectiveness study in the general population, patients with Roux-en-Y gastric bypass had a greater mean weight loss (25.5%) than patients with sleeve gastrectomy (18.8%) at 5-year follow-up (20). A previous meta-analysis showed that there were also better results at 5-year follow-up for Roux-en-Y gastric bypass compared to sleeve gastrectomy regarding not only weight loss but also remission of comorbidities such as hypertension, dyslipidemia, and type 2 diabetes (19). The number of events in patients was too low in our study to compare decline in comorbidities between the 2 types of surgery. In the general population, Roux-en-Y gastric bypass patients had, on the other hand, a higher 30-day rate of major adverse events than those undergoing sleeve gastrectomy (5.0% vs 2.6%) (20). It seems that craniopharyngioma patients have a higher risk of postoperative adverse events than the general population, as 5 (31%) patients had problems shortly after surgery, of whom 2 (13% of craniopharyngioma bariatric surgery patients) had serious adverse events. The risk-benefit ratio must especially be taken into account when applying bariatric surgery to underaged patients who may be unable to make a proper informed decision. Considering our patients had similar weight loss compared to controls after sleeve gastrectomy and their weight reduction was similar after sleeve gastrectomy compared to Roux-en-Y gastric bypass as well as the lower adverse event rate with sleeve gastrectomy in the general population, sleeve gastrectomy may be considered a more advantageous strategy in patients with craniopharyngioma. Our study did not include laparoscopic gastric banding (LAGB), which is another bariatric surgery procedure (16). One patient included in our study underwent a previous unsuccessful LAGB. Weismann et al. reported on 3 out of 6 patients with LAGB who needed another bariatric surgery procedure (16, 25). LABG appears a less effective option in these patients (25). Adjustable gastric banding is less effective in the general population as well: The PCORnet study described a mean 5-year weight loss of 12% for LAGB, vs 26% after Roux-en-Y gastric bypass, and 19% for sleeve gastrectomy (20). Only one patient was described to have had a

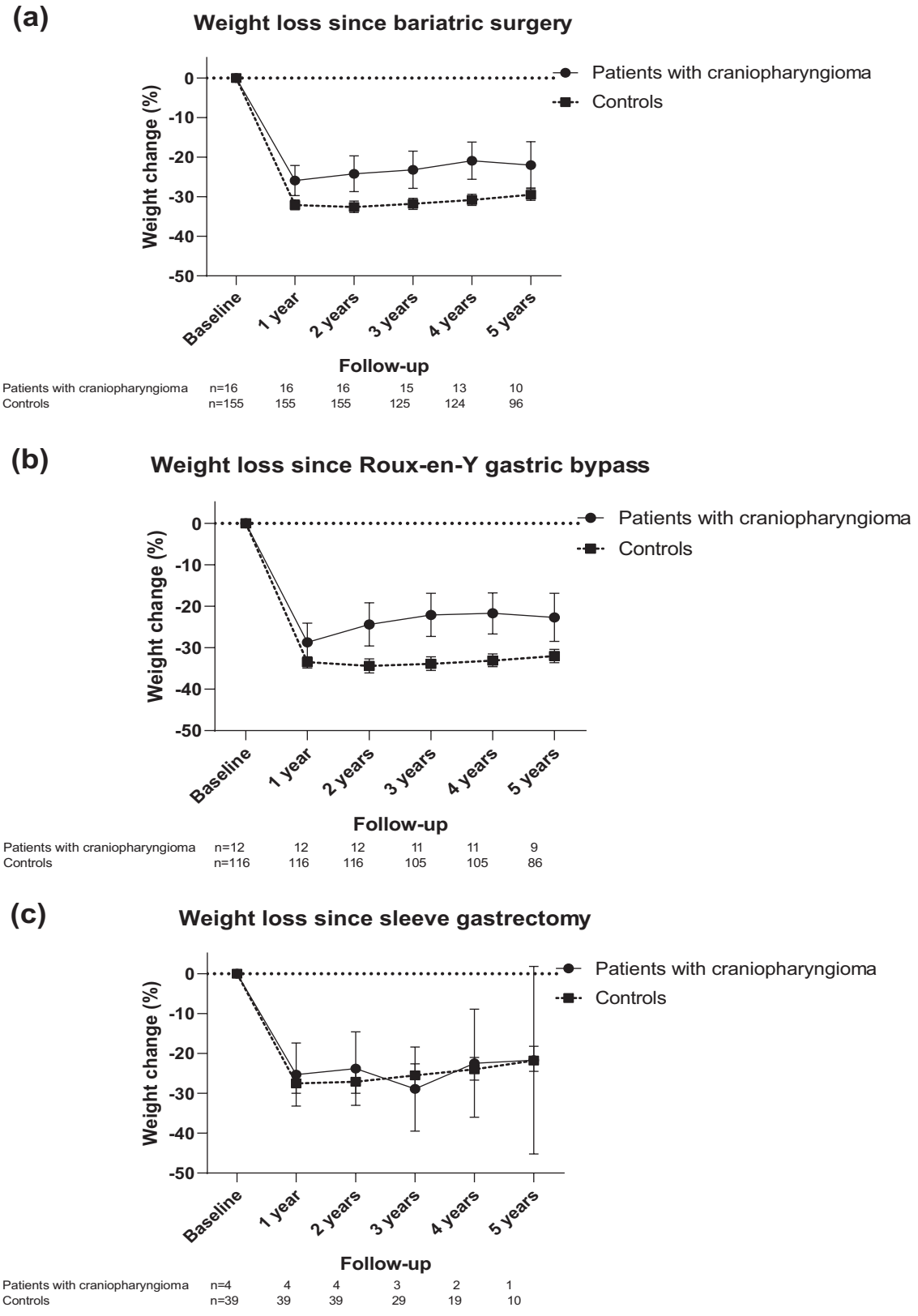

Figure 1. Weight loss up to 5-year follow-up after bariatric surgery. Mean (SD) percentage weight loss in obese craniopharyngioma patients and matched controls after A, any bariatric surgery; B, Roux-en-Y gastric bypass specifically; and C, sleeve gastrectomy specifically.

biliopancreatic diversion (25). In the general population, biliopancreatic diversion is not often performed because it is accompanied by very high rates of severe nutritional deficiencies and high rates of revisions (26).

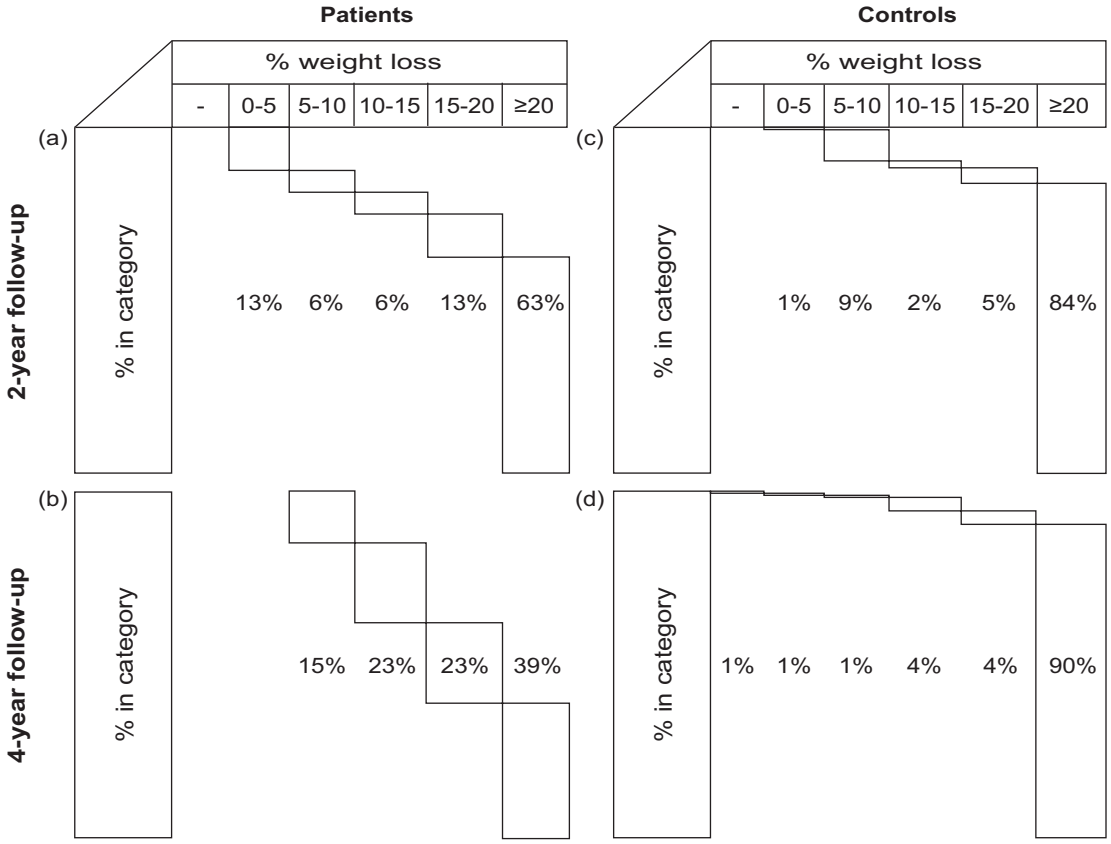

Figure 2. Waterfall plots of weight loss categories at 2- and 4-year follow-up after bariatric surgery. Percentage of obese craniopharyngioma patients (A and B, n = 16) and matched controls (C and D, n = 155) in 5% weight loss categories for interpolated data at A and C, 2-year; and B and D, 4-year follow-up after bariatric surgery. Percentages may not add up to 100% exactly because of rounding. Missing data at 4-year follow-up in 3 patients and 1 control.

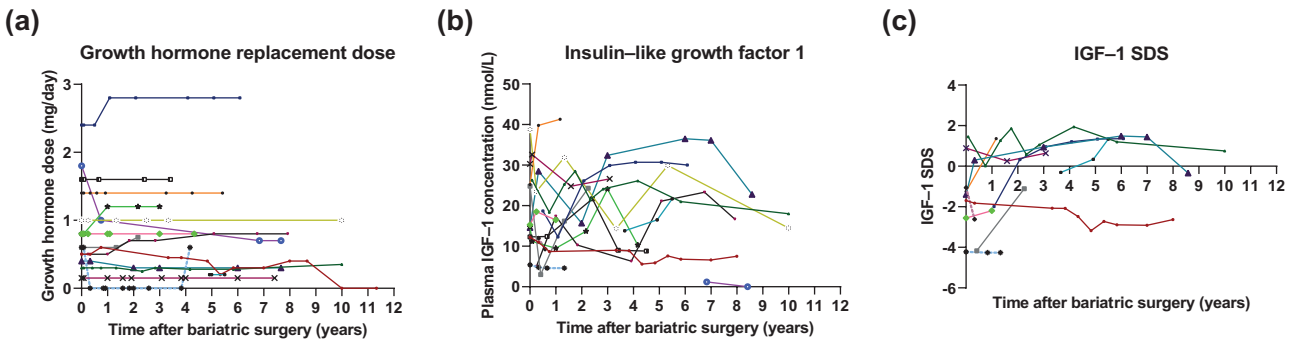

Figure 3. Change in growth hormone replacement therapy and insulin-like growth factor-1 (IGF-1) in obese craniopharyngioma patients following bariatric surgery. Spaghetti plots of changes in A, growth hormone replacement therapy daily dose; B, plasma IGF-1; and C, IGF-1 SDS for individual patients following bariatric surgery. A continuous line between observations represents patients using growth hormone replacement therapy, and an interrupted line indicates patients who did not use growth hormone at last follow-up.

Although individual patients required adjustments of hormone replacement therapy during follow-up, mean doses did not change significantly. Despite growth hormone being administered subcutaneously and thus not being absorbed in the intestine, it is unsurprising some dose changes were needed during follow-up because growth hormone doses are known to be influenced by age and BMI (27). Weight-based regimens have been proposed for glucocorticoid replacement, growth hormone replacement, and thyroid hormone replacement (27, 28). Changes in hormone replacement therapy can be considered as part of long-term practice in the care of patients with hypopituitarism and are expected in the case of weight change; this did not lead to any confirmed

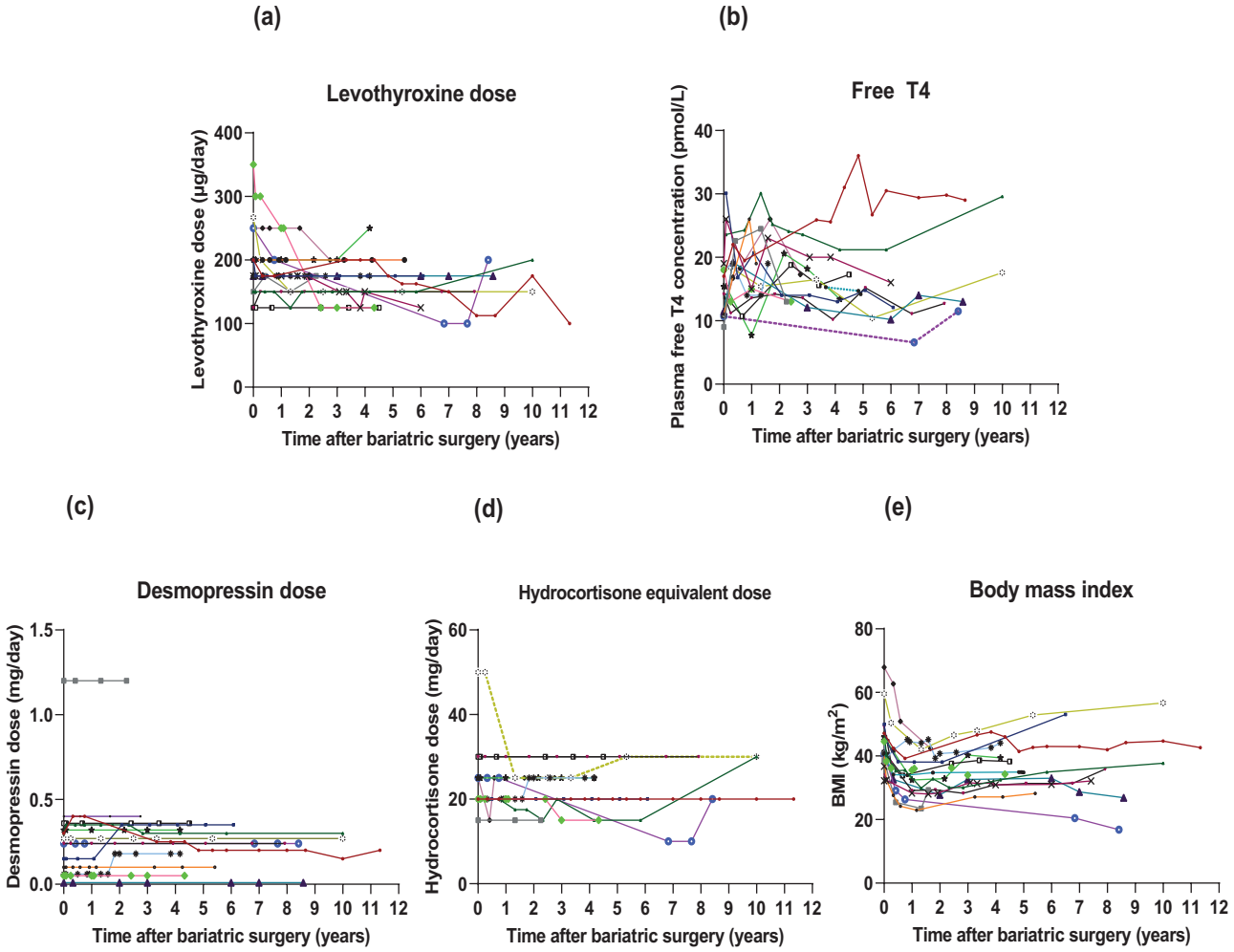

Figure 4. Change in pituitary hormone replacement therapy, free thyroxine (T4), and body mass index (BMI) in obese craniopharyngioma patients following bariatric surgery. Spaghetti plots of changes in daily A, levothyroxine dose; B, plasma free T4 concentration; C, daily desmopressin dose; D, daily hydrocortisone dose; and E, BMI for individual patients following bariatric surgery. A continuous line between observations represents patients with a deficiency for the particular pituitary hormone axis using hormone replacement therapy at last follow-up; an interrupted line is shown for patients who have a deficiency but do not use hormone replacement therapy at last follow-up; and a dotted line represents patients not known with this particular pituitary deficiency at last follow-up.

major adverse events such as acute adrenal crisis. Our results suggest that bariatric surgery can be regarded as safe for patients with hypopituitarism and complementary replacement therapy, which is in line with previous research that found no major negative effects regarding hormone replacement therapy (17, 18, 29, 30). Wolf and colleagues (18) performed an oral thyroid/hydrocortisone/paracetamol absorption test in a patient who had undergone gastric bypass surgery and found sufficient gastrointestinal drug absorption. Hence, additional emphasis on individual drug management and adjustments, especially shortly after bariatric surgery, seems important (29).

A limitation of our study is the retrospective design. Nevertheless, the study has several strengths. For such a rare disease, we report the largest sample size in the history of studies investigating bariatric surgery after craniopharyngioma and our study is unique in its duration of long-term follow-up. In addition, the cases were matched almost perfectly to controls from an average obese noncraniopharyngioma bariatric surgery population, thereby enabling an optimal comparison. Future research could investigate whether our data can be generalized to individuals with other causes of hypothalamic dysfunction.

Future studies that include even more patients and a longer follow-up as well as investigating differences between responders and nonresponders to bariatric surgery with respect to weight loss will be able to show whether the observations from our study are sustained over time. Sleeve gastrectomy combines restriction of food intake with favorable hormonal alterations and Roux-en-Y gastric bypass adds a component of mild malabsorption to that in

the general obese population (29). As our study shows a similar weight loss effect in patients compared to controls with respect to sleeve gastrectomy but not after Roux-en-Y gastric bypass, it would be of interest to measure hormonal changes, such as GLP-1, related to bariatric surgery in future studies (14). This would not only provide insight into the changed pathophysiology in patients with craniopharyngioma and hypothalamic dysfunction but also contribute to the exploration of other weight-loss strategies for obesity in these patients, such as GLP-1 analogues (31). In a small study of 10 patients with different causes of hypothalamic obesity, treatment with the GLP-1 analogue exenatide resulted in weight stabilization or decrease (31). It might also contribute to strategies to maintain weight loss after bariatric surgery: For example, the GLP-1 analogue liraglutide provided weight loss in a patient with craniopharyngioma whose bariatric surgery failed to be effective long term (32).

In conclusion, patients with craniopharyngioma had a mean weight loss of 21% up to 5 years after bariatric surgery. Although weight loss was significantly less compared to matched obese controls, this was a clinically relevant reduction. Weight loss was only less in patients who underwent Roux-en-Y gastric bypass surgery, while it was similar in those who underwent sleeve gastrectomy, compared to controls. Weight loss appears independent of bariatric surgery type. As for all patients with hypopituitarism, craniopharyngioma patients needed endocrinological follow-up and guidance with special attention for dose adjustment of their hormonal replacement therapy after bariatric surgery, but in this retrospective analysis no major changes were made in terms of dose and type of treatment. There were no confirmed cases of adrenal insufficiency. Bariatric surgery can therefore be regarded as a relatively safe and efficacious option in patients with craniopharyngioma who have no or mild cognitive decline and can cope with lifestyle restrictions after a bariatric procedure. The possible downsides of bariatric surgery in craniopharyngioma patients are suboptimal weight loss compared to controls and the potential for absorption problems and perhaps more postoperative problems, which should be thoroughly discussed with patients before proceeding with this invasive intervention (3).

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Data Availability: Data will not be shared to protect the anonymity and privacy of our patients. Because craniopharyngioma is a rare disease and only a few patients with this disease had bariatric surgery, providing raw data could expose the identity of our patients relatively easily.

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