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

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ABSTRACT

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

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

Design: Retrospective case control study.

Setting: Multicenter international study.

Patients and participants: Obese craniopharyngioma patients (N = 16; of which 12 women) with a history of bariatric surgery [12 Roux-en-Y gastric bypass, 4 sleeve gastrectomy; median age of 21 years (range 15-52), median follow-up 5.2 years (range 2.0-11.3)] and age/sex/surgery/BMI-matched obese controls (N = 155).

Main outcome measures: 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 versus 29.5% (28.0, 30.9) in controls (P = 0.02), which was less after Roux-en-Y gastric bypass (22.7% [16.9, 28.5] vs. 32.0% [30.4, 33.6]; P = 0.003) but at a similar level after sleeve gastrectomy (21.7% [-1.8, 45.2] vs. 21.8% [18.2, 25.5]; P = 0.96). No major changes in endocrine replacement therapy were observed after surgery. One patient died (unknown cause). One patient had long-term absorptive problems.

Conclusions: 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 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
Introduction

Craniopharyngiomas are rare brain tumors, which 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).

Besides 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).

Since 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 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 is 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 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 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 ~20 months after a sleeve gastrectomy due to insufficient weight loss and abdominal pain, and one patient had a Roux-en-Y gastric bypass ~6 years after gastric banding (the gastric banding was removed after 1 week due to abdominal complaints). Data from the second bariatric surgery onwards 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 pre-selected from the total cohort of 75,600 SOReg participants after exclusion of subjects who were not Swedish, were reoperated, had surgery before 2007, or had a procedure other than gastric bypass surgery or sleeve gastrectomy. Controls had follow-up data on body weight (kg) available at 6 weeks, and at 1, 2, and 5 years after bariatric surgery. Patients had a considerable variation in follow-up duration due to the retrospective design. Missing data for 3- and 4-year follow-up in controls and 1- to 5-year follow-up in patients was interpolated linearly between the two 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), pre-operative type 2 diabetes, and pre-operative hypertension. Further matching was performed by year of obesity operation (10-year span category), age at obesity operation (10-year span category), and pre-operative body mass index (BMI) (maximum of ±5 kg/m² different from the control). Controls were included only once. If less than ten 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 five patients. For one patient, the
criteria for BMI were extended as this patient was an outlier due to extremely high BMI: the best-matched controls were chosen without a limit to BMI criteria. Ultimately, all patients were each matched with ten controls except for two patients: nine controls were found for one and six controls were found for the extreme outlier. This resulted in the selection of 155 optimally matched controls (mean BMI difference −1.1 kg/m²; maximum BMI difference between patient and control ranging from 0.04 to 12.6 kg/m²).

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, standardized deviation 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, Chicago, IL). Continuous data are represented as mean ± standard deviation (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’s exact test for continuous and categorical data, respectively. Related continuous data were evaluated with Wilcoxon’s rank test. A two-way analysis of variance 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 subject (patient with craniopharyngioma or control) as the independent variable in the two-way ANOVA. Bootstrapping with 1,000 replicates was performed to meet the normality assumption related to the two-way analysis of variance 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 (<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 nine patients (56%) had residual tumor tissue on their last magnetic resonance imaging (MRI) scan. All patients had signs of either hypothalamic damage or third-ventricle involvement on MRI (n = 13 [87%, data missing for 1 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 four patients (25%) underwent sleeve gastrectomy. Median follow-up duration of the patients since bariatric surgery was 5.8 years (range 2.0–11.3), 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; $P = 0.03$) and more frequent presence of dyslipidemia before surgery (4/16 [25%] in patients vs. 6/155 [4%] in controls; $P = 0.008$); 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%]; $P = 0.001$). 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%]; $P = 0.03$).

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% (28.0, 30.9) in controls ($P = 0.02$; 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% [30.4, 33.6]; $P = 0.003$) but was comparable at 5-year follow-up after sleeve gastrectomy comparing patients and controls, respectively (21.7% [−1.8, 45.2] vs. 21.8% [18.2, 25.5], $P = 0.96$). 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]; $P < 0.001$), 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, eight (50%) of 16 patients had lost at least 20% of their original body weight, three (19%) between 10% and 15%, three (19%) between 5% and 10%, and one (6%) <5% weight loss, while one (6%) showed weight increase. Among the patients who used sibutramine, one had at least 20% weight reduction and the other had 5–10% 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]; \( P = 0.23 \), one missing) and those with (\( n = 7 \)) and without (\( n = 9 \)) radiotherapy (16.6% [16.9] vs .23.5% [15.7]; \( P = 0.41 \)), 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 subjects 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%; \( P = 0.008 \)) and at last follow-up (2/15 [13%; one missing data] vs. 2/155 [1%; \( P = 0.04 \)). Hypertension occurred at a similar prevalence in patients and controls before bariatric surgery (4/16 [25%] vs. 35/155 [23%; \( P = 0.76 \)) and there was no significant difference at last follow-up (0/16 [0%] vs. 18/155 [12%; \( P = 0.22 \)), although all cases of hypertension in patients were resolved at last follow-up.

**Complications after Bariatric Surgery**

Five patients experienced short-term peri- and post-operative complaints or issues: post-operative abdominal pain (\( n = 1 \)), dumping syndrome (\( n = 1 \)), inability to eat solid food due to abdominal fullness (\( n = 1 \)), stenosis of the anastomosis (\( n = 1 \)), a generally complicated post-operative course with nephrolithiasis, pulmonary embolism, and post-infarction 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 the age of 32 years, approximately 2.5 years after their second bariatric surgery; the cause of death was unknown. Since the cause 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 only receiving growth hormone replacement therapy (see Table 1 for baseline pituitary deficiencies, and Fig. 3-4 for individual changes of replacement therapy). All patients were growth hormone deficient. Mean daily growth hormone dose was not significantly different before bariatric surgery versus last follow-up (0.92 [SD 0.65] vs. 0.72 [0.88] mg; \( P = 0.50 \)); similarly, mean IGF-1 (19.4 [10.1] vs. 34.0 [57.6] nmol/L; \( P = 0.72 \)) and mean IGF-1 SDS values (–1.6 [1.6] vs. –0.7 [2.0]; \( P = 0.61 \)) did not change significantly (Fig. 3). One patient did not initially receive growth hormone replacement therapy due to 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 of which was due to diagnosis of a malignancy (Fig. 3).

Fourteen (88%) of 16 patients had a gonadal hormone deficiency; eight had no change in their replacement therapy and one 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 due to a liver adenoma.

Thyroid hormone replacement therapy was needed in 15 (94%) of 16 patients, of which five had no changes in thyroid medication at all (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; \( P = 0.23 \)). 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; \( P = 0.29 \)). DDAVP dose was unchanged in ten patients (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; \( P = 0.85 \)).

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 ~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, only observed 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 current 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 two 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 post-operative adverse events than the general population, as five (31%) patients had problems shortly after surgery, of which two (13% of craniopharyngioma bariatric surgery patients) were 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 discussion. 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, which is another bariatric surgery procedure (16). One patient included in our study was subject to a previous unsuccessful laparoscopic gastric banding (LAGB). Weismann et al. reported on 3 out of 6 described patients with LAGB that 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 five-year weight loss of 12% for LAGB, versus 26% after Roux-en-Y gastric bypass, and 19% for sleeve gastrectomy (20). Only one patient was described to have had a biliopancreatic diversion (25). In the general population, biliopancreatic diversion is not often performed as it is accompanied with very high rates of severe nutritional deficiencies and high rates of revisions (26).

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 as 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 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.
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 non-craniopharyngioma bariatric surgery population, thereby enabling an optimal comparison. Future research could investigate whether our data can be generalized to subjects 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 non-responders 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 ten 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 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. Since craniopharyngioma is a rare disease and only few patients with this disease had bariatric surgery, providing raw data could expose the identity of our patients relatively easily.

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S.S.v.S., P.W., N.K., C.B., H.B., M.W., V.W., and D.S.O. gathered and/or delivered data. S.J.C.M.M.N. conceived the original idea and designed the study. D.S.O. and S.J.M.M.N. developed the theory. D.S.O. supervised the project and helped shape the research. D.S.O. and S.S.v.S. have accessed verified the underlying data. S.S.v.S. was in charge of overall communications and planning. P.W., N.K., C.B., H.B., M.F., M.W., V.W., M.M.v.d.H.E., G.J., A.L., M.K., M.B., P.J.D.D., S.J.M.M.N., and D.S.O. provided critical feedback. M.M.v.d.H.E., A.J.v.d.L., G.J., A.L., M.K., M.B., and P.J.D.D. helped shape the research. M.M.v.d.H.E. and A.J.v.d.L. supervised the project. M.W. provided help with analysis and designing the study. M.F. supported and checked analytic calculations. S.S.v.S. wrote the manuscript, performed data management, and performed the analysis. H.B. helped writing the manuscript. All authors approved the final version, had access to the full data in the study and accept responsibility to submit for publication.
Declaration of Interests.

A.L. reports personal fees from payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events, personal fees from support for attending meetings and/or travel, personal fees from participation on a data safety monitoring board or advisory board, outside the submitted work. S.S.v.S. reports personal fees from Support for PhD thesis printing and defense, personal fees from support for attending meetings and/or travel, fee to Stichting Research Klinische Endocrinologie from participation on Acrodat enrolment, outside the submitted work. M.K. reports grants and/or personal fees from Sanofi, AstraZeneca, Fit for Me, Lilly, Novo Nordisk, and Ipsen outside the submitted work.
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FIGURE LEGEND

Figure legends

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 any bariatric surgery (A), Roux-en-Y gastric bypass specifically (B), and sleeve gastrectomy specifically (C).

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

Figure 3: Change in growth hormone replacement therapy and IGF-1 in obese craniopharyngioma patients following bariatric surgery
Spaghetti plots of changes in growth hormone replacement therapy daily dose (A), plasma IGF-1 (B), and IGF-1 SDS (C) 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. IGF-1=insulin-like growth factor 1; SDS=standardised deviation score.

Figure 4: Change in pituitary hormone replacement therapy, free T4, and BMI in obese craniopharyngioma patients following bariatric surgery
Spaghetti plots of changes in daily levothyroxine dose (A), plasma free T4 concentration (B), daily desmopressin dose (C), daily hydrocortisone dose (D), and BMI (E) 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. BMI=body mass index, T4=thyroxine.
Table 1—Baseline demographic and clinical characteristics of patients with craniopharyngioma

| Characteristic                                                                 | Craniopharyngioma patients (N = 16)               |
|--------------------------------------------------------------------------------|---------------------------------------------------|
| **Sex, n (%)**                                                                |                                                  |
| Women                                                                          | 12 (75)                                          |
| Men                                                                            | 4 (25)                                           |
| **Median (range) age at first craniopharyngioma treatment (years)**            | 12 (4–48)                                        |
| **Median age (range) at last follow-up (years)**                               | 33 (17–61)                                       |
| **Mean (SD) follow-up duration since craniopharyngioma surgery at last follow-up (years)** | 11.9 ± 3.8                                        |
| **Treatment for craniopharyngioma, n (%)**                                     |                                                  |
| Surgery                                                                        |                                                  |
| Initially*                                                                     | 15 (94)                                          |
| Ever                                                                           | 15 (94)                                          |
| Median (range) number of craniopharyngioma surgeries                           | 1 (1–6)                                          |
| **Radiotherapy**                                                               |                                                  |
| Initially (in addition to surgery)                                             | 2 (13)                                           |
| Ever                                                                           | 7 (44)                                           |
| Mean (SD) cumulative radiotherapy dose (mGy)                                   | 4,225 ± 1,801                                    |
| **Hypothalamic damage, n (%)**                                                 |                                                  |
|                                                                                | 9 (60)                                            |
| **Third-ventricle involvement, n (%)**                                         | 9 (60)                                            |
| **Hypothalamic damage and/or third-ventricle involvement, n (%)**              | 13 (87)                                          |
| **Hypothalamic damage and/or third-ventricle involvement and/or radiotherapy, n (%)** | 16 (100)                                        |
| **Pituitary deficiencies**                                                     |                                                  |
| GH deficiency                                                                  |                                                  |
| Frequency, n (%)                                                               | 16 (100)                                         |
| Median (range) age at occurrence (years)                                       | 13 (6–49)                                        |
| GH replacement therapy at last follow-up, n (%)                                | 14 (88)                                          |
| TSH deficiency                                                                 |                                                  |
| Frequency, n (%)                                                               | 15 (94)                                          |
| Median (range) age at occurrence (years)                                       | 14 (4–48)                                        |
| **Gonadal axis deficiency**                                                    |                                                  |
| Frequency, n (%)                                                               | 14 (88)                                          |
| Median (range) age at occurrence (years)                                       | 13 (6–48)                                        |
| **ACTH deficiency**                                                            |                                                  |
| Frequency, n (%)                                                               | 12 (75)                                          |
| Median (range) age at occurrence (years)                                       | 12 (4–48)                                        |
| **ADH deficiency**                                                             |                                                  |
| Frequency, n (%)                                                               | 14 (88)                                          |
| Median (range) age at occurrence (years)                                       | 12 (4–48)                                        |
| **Use of antiepileptic drugs, n (%)**                                          | 2 (13)                                           |
| **Bariatric procedure**                                                        |                                                  |
| Median (range) age at bariatric surgery (years)                                 | 21 (15–52)                                       |
| Mean (SD) BMI before bariatric surgery (kg/m²)                                  | 46.0 ± 8.0                                       |
| Median (range) follow-up since bariatric procedure (years)                     | 5.8 (2.0–11.3)                                   |

ACTH, adenocorticotropic hormone; ADH, antidiuretic hormone; BMI, body mass index; GH, growth hormone; TSH, thyroid-stimulating hormone. *Excluding one patient treated with cyst aspiration initially.
Table 2–Baseline characteristics of patients treated with bariatric surgery: craniopharyngioma-related hypothalamic obesity versus controls with 'common' obesity

| Characteristic                                  | Craniopharyngioma patients (N = 16) | Matched controls (N = 155) |
|-------------------------------------------------|-------------------------------------|---------------------------|
| Sex, n (%)                                       |                                     |                           |
| Female                                          | 12 (75)                             | 119 (77)                  |
| Male                                            | 4 (25)                              | 36 (23)                   |
| Mean (SD) age at bariatric surgery (years)       | 26.4 ± 12.1                         | 30.5 ± 11.5*              |
| Bariatric procedure, n (%)                       |                                     |                           |
| Roux-en-Y gastric bypass                        | 12 (75)                             | 116 (75)                  |
| Sleeve gastrectomy                              | 4 (25%)                             | 39 (25)                   |
| Mean (SD) preoperative BMI (kg/m²)              | 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                |
| Pre-operative diabetes mellitus, n (%)          | 1 (6)                               | 10 (6)                    |
| Pre-operative hypertension, n (%)               | 4 (25)                              | 35 (23)                   |
| Pre-operative dyslipidemia, n (%)               | 4 (25)                              | 6 (4)*                    |

BMI, body mass index. *P = 0.03, †P = 0.008.
Table 3–Percentage weight loss after bariatric surgery of patients with craniopharyngioma and matched controls

| Time after surgery | Sleeve gastrectomy | Roux-en-Y gastric bypass | Any bariatric surgery procedure |
|-------------------|--------------------|--------------------------|--------------------------------|
|                   | % Weight loss (95% CI) | % Weight loss (95% CI) | % Weight loss (95% CI) |
| **Patients**      | **Controls** | **Patients** | **Controls** | **Patients** | **Controls** |
| 6 weeks           | 18.1 (12.5, 23.7) | 14.7 (12.9, 16.5) | 0.25 | 15.0 (12.1, 18.0) | 15.5 (14.6, 16.4) | 0.74 | 15.8 (13.2, 18.4) | 15.3 (14.5, 16.1) | 0.71 |
| 1 year            | 25.3 (17.4, 33.2) | 27.5 (25.0, 30.0) | 0.60 | 28.7 (24.1, 33.4) | 33.5 (32.2, 34.9) | 0.05 | 25.9 (22.1, 29.7) | 32.1 (30.8, 33.3) | 0.003 |
| 2 years           | 23.8 (14.6, 33.0) | 27.1 (24.1, 30.0) | 0.50 | 24.4 (19.2, 29.6) | 34.4 (32.7, 36.1) | <0.001 | 24.2 (19.7, 28.7) | 32.6 (31.1, 34.0) | 0.001 |
| 3 years           | 28.9 (18.4, 39.5) | 25.5 (22.6, 28.4) | 0.53 | 22.1 (16.9, 27.3) | 33.9 (32.2, 35.5) | <0.001 | 23.2 (18.5, 27.9) | 31.8 (30.4, 33.2) | 0.001 |
| 4 years           | 22.5 (8.9, 36.0)  | 24.0 (21.0, 26.7) | 0.82 | 21.7 (16.8, 26.7) | 33.1 (31.5, 34.6) | <0.001 | 20.9 (16.2, 25.6) | 30.8 (29.4, 32.2) | <0.001 |
| 5 years           | 21.7 (−1.8, 45.2) | 21.8 (18.2, 25.5) | 0.96 | 22.7 (16.9, 28.5) | 32.0 (30.4, 33.6) | 0.003 | 22.0 (16.1, 27.8) | 29.5 (28.0, 30.9) | 0.02 |
(a) Weight loss since bariatric surgery

Patients with craniopharyngioma: n=16
Controls: n=155

Follow-up:

Baseline 1 year 2 years 3 years 4 years 5 years
Patients with craniopharyngioma: 16 16 15 13 10
Controls: 155 155 125 124 96

(b) Weight loss since Roux-en-Y gastric bypass

Patients with craniopharyngioma: n=12
Controls: n=116

Follow-up:

Baseline 1 year 2 years 3 years 4 years 5 years
Patients with craniopharyngioma: 12 12 11 11 9
Controls: 116 116 105 105 86

(c) Weight loss since sleeve gastrectomy

Patients with craniopharyngioma: n=4
Controls: n=39

Follow-up:

Baseline 1 year 2 years 3 years 4 years 5 years
Patients with craniopharyngioma: 4 4 3 2 1
Controls: 39 39 29 19 10
Patients

| % weight loss | - | 0-5 | 5-10 | 10-15 | 15-20 | ≥20 |
|---------------|---|-----|------|-------|-------|-----|
| % in category | 13% | 6% | 6% | 13% | 63% |

Controls

| % weight loss | - | 0-5 | 5-10 | 10-15 | 15-20 | ≥20 |
|---------------|---|-----|------|-------|-------|-----|
| % in category | 1% | 9% | 2% | 5% | 84% |

2-year follow-up

4-year follow-up

(a) 13% 6% 6% 13% 63%
(b) 15% 23% 23% 39%
(c) 1% 9% 2% 5% 84%
(d) 1% 1% 1% 4% 4% 90%
Growth hormone replacement dose

Insulin–like growth factor 1

IGF–1 SDS
