Bariatric surgery for treatment of hypothalamic obesity after craniopharyngioma therapy: a matched case-control study

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Preface

This dissertation is part of the requirements for the degree of Master of Medicine in Medicine at Ghent University and is fulfilled in association with Ghent University Hospital. This requirement enables students to get a glimpse of scientific research and gives the opportunity to profoundly expand knowledge in a chosen field of interest. Therefore, I would like to express my sincere gratitude to the people making this opportunity possible.

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Abstract

Background Craniopharyngioma and its treatment can lead to significant weight gain and can cause multiple pituitary hormone deficiencies due to disturbance of the hypothalamo-pituitary region leading to increased morbidity and mortality. As hypothalamic obesity is mainly resistant to conservative treatment, bariatric surgery, proven to be effective in common obesity, could be a therapeutic option. However, limited studies concerning this topic have been published. The objective of this study was to investigate the efficacy in terms of weight loss and safety in terms of effects of bariatric surgery on hormone replacement therapy in patients with hypothalamic obesity after craniopharyngioma treatment during 2 years of follow-up.

Methods This retrospective matched case-control study involved five patients treated with sleeve gastrectomy (N=2) or Roux-en-Y gastric bypass (N=3) at Ghent University Hospital for hypothalamic obesity following treatment of a craniopharyngioma who were individually matched to two surgically treated obese control patients with no hypothalamic dysfunction. Percentage of total bodyweight loss since bariatric surgery was estimated in both groups at 3, 6, 12 and 24 months after surgery and differences in weight loss were compared to baseline between both groups. In addition, remission or improvement of diabetes mellitus type 2 and hyperlipidaemia in patients treated for craniopharyngioma at 12 and 24 months after surgery was reported. Finally, alterations in hormone replacement therapy at 6, 12 and 24 months after bariatric surgery in patients treated for craniopharyngioma were documented.

Results Estimated mean weight loss 2 years after bariatric surgery in patients with hypothalamic obesity after craniopharyngioma treatment compared to baseline was 14,7% (p<0,01). Estimated mean difference in weight loss at 2 years of follow-up compared to baseline between patients with hypothalamic obesity after craniopharyngioma treatment and patients with non-hypothalamic obesity was 13,6% (p<0,05). At 2 years of follow-up, remission of type 2 diabetes mellitus was observed in one out of two patients treated for a craniopharyngioma. Hypertriglycerideremia in the only hyperlipidaemic patient treated for a craniopharyngioma did not resolve. All patients had panhypopituitarism including diabetes insipidus. Minor alterations in hormone replacement therapy after bariatric surgery were observed in all five patients.
Conclusion At 2 years of follow-up, bariatric surgery led to a greater weight loss compared to baseline in patients with non-hypothalamic obesity than in patients with hypothalamic obesity after treatment of a craniopharyngioma. Even so, significant weight loss after bariatric surgery in patients with hypothalamic obesity after craniopharyngioma therapy was plausible. Bariatric surgery seemed to be safe in terms of its effect on hormone replacement therapy.
Samenvatting

Achtergrond Een craniofaryngeoom en bijhorende behandeling kunnen leiden tot gewichtstoename en deficiënties van een of meerdere hypofysaire hormonen door aantasting van de hypothalamo-hypofysaire regio leidend tot een stijging in morbiditeit en mortaliteit. Aangezien obesitas door hypothalamo dysfunctie voornamelijk resistent is aan conservatieve behandeling, zou bariatrische heelkunde aangewezen kunnen zijn omwille van bewezen effectiviteit in patiënten met exogene obesitas. Echter, er is beperkte literatuur omtrent dit onderwerp. Het doel van deze studie was daarom de effectiviteit van bariatrische heelkunde inzake gewichtsverlies en de veiligheid inzake het effect van bariatrische heelkunde op de behandeling van hypopituïtarisme in patiënten met hypothalamo obesitas na behandeling van een craniofaryngeoom te analyseren.

Methodologie Dit retrospectief patiënten-controleonderzoek identificeerde vijf patiënten behandeld in het Universitair Ziekenhuis te Gent met een sleeve gastrectomie (N=2) of een Roux-en-Y gastric bypass (N=3) voor hypothalamo obesitas na behandeling van een craniofaryngeoom. De vijf patiënten werden elk individueel gekoppeld aan twee heelkundig behandelde patiënten met obesitas zonder hypothalamo dysfunctie. Percentage gewichtsverlies op 3, 6, 12 en 24 maanden na heelkunde werd berekend en verschillen in gewichtsverlies ten opzichte van het preoperatief gewicht werden tussen beide groepen vergeleken. Remissie of regressie van diabetes mellitus type 2 en hyperlipidemie op 12 en 24 maanden na heelkunde in patiënten behandeld voor een craniofaryngeoom werd geobserveerd. Daarnaast werden aanpassingen aan de behandeling voor hypopituïtarisme op 6, 12 en 24 maanden na bariatrische heelkunde in patiënten behandeld voor een craniofaryngeoom gedaocumenteerd.

Resultaten Het geschat gemiddeld gewichtsverlies 2 jaar na bariatrische heelkunde in patiënten met hypothalamo obesitas na behandeling van een craniofaryngeoom was 14,7% (p<0,01). Het geschat gemiddeld verschil in gewichtsverlies 2 jaar na bariatrische heelkunde tussen patiënten met hypothalamo obesitas na behandeling van een craniofaryngeoom en patiënten met non-hypothalamo obesitas was 13,6% (p<0,05). Remissie van diabetes mellitus type 2 na heelkunde werd geobserveerd in één van twee patiënten met diabetes mellitus type 2 en behandeld voor een craniofaryngeoom. Hypertriglyceridemie in de enige patiënt behandeld voor een craniofaryngeoom en gediagnosticeerd met hyperlipidemie ging niet in remissie na heelkunde. Alle patiënten behandeld met een craniofaryngeoom werden
gediagnosticeerd met panhypopituïtarisme inclusief diabetes insipidus. Kleine aanpassingen in de behandeling van hypopituïtarisme werden gedocumenteerd in alle patiënten.

**Conclusie** Bariatrische heelkunde gaf aanleiding tot een groter gewichtsverlies 2 jaar na heelkunde in patiënten met non-hypothalamo obesitas ten opzichte van patiënten met hypothalamo obesitas door behandeling van een craniofaryngeoom. Doch, een significant gewichtsverlies in patiënten met hypothalamo obesitas na behandeling van een craniofaryngeoom was mogelijk. Bariatrische heelkunde bleek veilig inzake het effect op de behandeling van hypopituïtarisme.
Introduction

1. Craniopharyngioma

1.1. Definition and epidemiology

A craniopharyngioma (CP) is an epithelial tumour with a benign histological appearance (WHO grade I) (1-3). These intracranial tumours arise along the craniopharyngeal duct, the canal connecting the stomodeal ectoderm with the evaginated Rathke’s pouch. Most of them are located in the sellar/parasellar region; the majority has a suprasellar component (1, 3). Craniopharyngiomas are rare, with an incidence of 1.3 cases per million persons per year. There is a bimodal age distribution, with one peak in children between 5 and 14 years of age, and a second peak in adults between 50 and 74 years of age (4). They account for 2–5% of all the primary intracranial neoplasms and 5.6–15% of the intracranial tumours in children (3, 5).

1.2. Diagnosis

Preoperatively, clinical presentation followed by magnetic resonance imaging (MRI) and/or computed tomography (CT) can lead to diagnosis of the craniopharyngioma (6). Postoperatively, the diagnosis can be confirmed by histology (7).

1.3. Treatment

The optimal treatment for patients with craniopharyngioma remains controversial. As tumour recurrence is closely related to the extent of surgical removal, complete tumour excision, evaluated by the absence of residual tumour on postoperative MRI imaging or CT scanning, could be the primary goal of treatment (8-12). Drainage of the cystic component can precede craniopharyngioma removal if clinical signs of severe hypothalamic derangement or visual loss are present (8). However, recent findings have documented that radical surgery has no impact on progression rates (13, 14). Also, there is a continued appreciation of the morbidity associated with aggressive surgery, particularly with regard to hypothalamic function. Removal of tumour adherent to the hypothalamus is associated with significant occurrence of morbidity such as severe weight gain (11, 15). Magnetic resonance imaging shows evidence of hypothalamic damage being correlated with obesity after craniopharyngioma resection (16). Thus, if there are risk factors such as symptoms of hypothalamic dysregulation at presentation, or if the tumour is found to be adherent to hypothalamic tissue at operation, a limited surgical
procedure could be considered to preserve the hypothalamus (8, 11-15). Postoperative radiotherapy can offer an alternative for prevention of tumour recurrence in these cases (8-12).

1.4. Mortality and morbidity

Craniopharyngiomas are associated with an increased overall mortality and decreased survival probability with an enhanced risk of cerebrovascular, cardiovascular and respiratory mortality (4, 8, 9, 17-22). Despite their benign histological appearance and overall survival rates being relatively high (2, 4, 8, 9, 17-22), due to proximity and pressure of the tumour or the damage by therapeutic interventions on fundamental neuronal structures such as the hypothalamo-pituitary system, craniopharyngiomas are associated with serious morbidity (8, 11-15). The most frequent clinical manifestations at presentation are non-specific symptoms of intracranial pressure such as headaches, visual dysfunction and hormone deficits. Most patients with CP present with one or more pituitary deficiencies including anterior pituitary hormones such as growth hormone (GH), gonadotropins, adrenocorticotropic hormone (ACTH) and thyroid-stimulating hormone (TSH), and/or diabetes insipidus (8-10, 18, 19, 23). Obesity tends to occur as a late manifestation, shortly before diagnosis (24). It can be seen in 10-12% of the patients with CP. On the contrary, weight loss as a clinical manifestation is also possible and occurs with a similar rate (9, 10, 18).

Long-term morbidity in patients treated for CP is substantial and adversely affects quality of life. The visual outcome in patients treated for CP is compromised in a considerable number of patients (10, 18, 19). Deterioration of neuropsychological and cognitive function contributes to the reduction of independence for basal daily activities negatively influencing professional occupation or school status (9, 10, 18, 19, 25). Furthermore, partial or complete hypopituitarism is seen in an important number of patients as new endocrine deficits may develop after surgery of CP and restoration of preoperative hormone deficits after a surgical intervention is frequently absent or uncommon (18, 26-29). However, one of the most frequent symptoms of hypothalamic disturbance due to tumour or treatment related hypothalamic damage, is excessive weight gain. The degree of obesity often increases early after CP treatment with rapid weight gain occurring 6-12 months after therapy (30-32); and is reported to be present in 39-66% of the treated patients (10, 18, 21, 23, 28, 30, 33, 34). Furthermore, craniopharyngioma survivors developing obesity have a greater morbidity and mortality than survivors with a normal weight (30).
2. Hypothalamic obesity

2.1. Central regulation of energy homeostasis and pathogenesis of hypothalamic obesity

Obesity could be defined as an unwanted positive energy balance with excessive fat accumulation in adipose tissue leading to health impairment and with excess of abdominal body fat as the greatest risk factor for adverse health consequences. Classified according to the body mass index (BMI), obesity is defined as BMI ≥ 30.0 kg/m² (35).

Disease processes which structurally impact the hypothalamus including craniopharyngioma with hypothalamic involvement or removal of CP adherent to the hypothalamus, lead to pathological weight gain termed as hypothalamic obesity (HyOb). As the hypothalamus integrates a variety of hormonal and neuropeptide signals informing the metabolic state of the organism and adjusts effector pathways to achieve energy homeostasis, it is a key element in bodyweight control which could clarify the association with pathological weight gain (13-15, 24, 30, 36, 37).

Circulating signals such as the pancreatic hormone insulin and leptin secreted by adipocytes, inform the brain of changes in body fat mass. In the energy replete state, both insulin and leptin are increased. They act in the hypothalamus by stimulating catabolic pathways – neurons in the arcuate nucleus (ARC) that express pro-opiomelanocortin (POMC) and cocaine- and amphetamine-regulated transcript (CART) – while inhibiting anabolic pathways – neurons in the ARC that express neuropeptide Y (NPY) and agouti-related protein (AgRP), thus resulting in a decreased appetite and food intake and anorexia (Fig. 1) (36, 37).
Other hormones involved in energy homeostasis including peptide YY (PYY) and ghrelin also exert their function on the hypothalamus. PYY is secreted from cells lining the distal small bowel and the colon. The levels of PYY increase after a meal to stop further food intake as PYY₃₋₃⁶, an anorectic isoform, inhibits NPY/AgRP neurons (38). Levels of ghrelin, secreted primarily by the stomach and duodenum, increase shortly before every meal and decrease shortly after every meal consistent with the urge to eat as it stimulates NPY/AgRP neurons (36, 37, 39).

These neurons project to second-order neurons present in several brain areas of energy regulation where the release of α-melanocyte stimulating hormone (α-MSH) (derived from POMC) reduces food intake and increases energy expenditure, while release of NPY stimulates eating and decreases energy expenditure (36, 37).

Furthermore, based on brain lesions and brain stimulation tests, some areas in the hypothalamus can be defined as mainly orexigenic, as lesions induce hyperphagia and obesity, while others are anorexigenic, as lesions cause anorexia and weight loss (36, 37).

CP appears to be a common cause of HyOb. A study shows that hypothalamic damage due to tumour or its treatment is the primary cause of obesity in children surviving brain tumours.
Accumulating evidence supports the fact that the damage caused by CP and its treatment results in dysfunction of normal homeostatic mechanisms and a disturbed appetite regulation. Failure of neuronal systems to respond to leptin signals leads to leptin resistance (37). Elevation of leptin levels after craniopharyngioma treatment in children has been noted, suggesting that the rise in leptin concentrations may be due to a disturbed feedback mechanism. Deficient signalling of leptin results in loss of NPY inhibition which could cause increased appetite (41).

However, analysis of energy intake shows no difference in children with HyOb compared to patients with simple obesity. Instead, energy expenditure is compromised which could suggest that a decrease of physical activity rather than hyperphagia contributes to obesity in craniopharyngioma patients (42). These findings have been substantiated in adults with childhood craniopharyngioma in whom basal metabolic rate is decreased and caloric intake is lower compared to matched controls (32). A reduced sympathetic tone has been suggested to contribute to the decrease in physical activity as urine catecholamine metabolites in patients with craniopharyngioma have been found to be lower than in BMI-matched control patients (43). Dextroamphetamine, sympathomimetic pharmacotherapy, used in obese paediatric patients after surgical resection for CP, stabilizes weight gain and improves activity (44). Alternatively, an increase in the parasympathetic nervous outcome could also contribute to the development of obesity. Rats with lesions in the ventromedial hypothalamus not only show signs of reduced sympathetic tone, the lesions also lead to disinhibition of the vagal tone, resulting in increased insulin secretion through stimulation of the pancreatic β-cells (45). Insulin hypersecretion has been demonstrated in children with hypothalamic obesity due to brain tumours or cranial irradiation (46). Supporting this assumption, octreotide, a somatostatin analogue, leads to reversal of weight gain due to reduction of insulin secretion (46, 47). Thus, the result of this disturbed sympathoadrenergic regulation and increased parasympathetic output is decreased energy expenditure with division of calories away from tissues such as muscles which consume energy, to depots of energy such as adipose tissue and therefore contributes to the pathological weight gain seen in hypothalamic obesity.

2.2. Risk factors for excessive weight gain

Some risk factors of development of obesity in patients treated for CP reiterate the importance of the hypothalamus in energy homeostasis. The grade of hypothalamic tumour involvement, the grade of hypothalamic damage due to therapeutic interventions evaluated on magnetic resonance imaging, and hypothalamic radiation doses of more than 51 gray (Gy) allow prediction of patients most at risk for postoperative weight gain (16, 24, 40, 48-52). The
endocrinopathy due to the disturbance of the hypothalamo-pituitary system further adds to the risk of weight gain (40). However, besides the effect of hypothalamo-pituitary disturbance, HyOb could also be exacerbated by other complications of CP or its treatment such as neurological deficits, visual deficits, psychological difficulties and increased daytime sleepiness which further adds to the restricted repertoire of movements (53). Other factors associated with significant hypothalamic morbidity include a higher BMI at diagnosis, a younger age at diagnosis, familial predisposition for obesity and initial symptoms of intracranial hypertension, tumour recurrence and multiple surgeries associated with hypothalamic lesions (24, 30, 31, 40).

2.3. Health consequences

Development of cardiovascular diseases is related to the degree of overweight as obesity can be an independent risk factor for cardiovascular morbidity and mortality. However, obesity also contributes to the occurrence of other cardiovascular risk factors. The risk of non-insulin-dependent diabetes mellitus and prediabetic conditions such as impaired glucose tolerance (IGT) and insulin resistance are associated with obesity and especially with the increase of intra-abdominal fat. Equally, as an increase in BMI is associated with an increase of systolic and diastolic blood pressure, obese patients are at a high risk of developing arterial hypertension (AHT). Also, dyslipidaemic disturbances including high plasma triglycerides (TG), and low high-density lipoprotein (HDL) levels are seen in obese patients. Furthermore, intra-abdominal fat leads to more low-density lipoprotein (LDL) particles (35).

Furthermore, obesity could also affect pulmonary function as a high BMI next to central obesity and neck size, results in the presence of sleep apnoea (35).

As obesity is a common morbidity seen in patients with craniopharyngioma, the health consequences associated with obesity could be present in this population as well. Sleep disordered breathing has been observed in craniopharyngioma patients and could be one of the factors contributing to the daytime sleepiness, a morbidity often seen in these patients (54, 55). Furthermore, it has been reported that childhood craniopharyngioma patients show more features of metabolic syndrome than BMI-matched controls (33, 56). Matched with healthy control patients, childhood CP patients have a higher abdominal fat and adverse lipid profile (33). Data on insulin dynamics are conflicting. Although a similar rate of insulin secretion and insulin sensitivity in patients treated for CP compared to BMI-matched controls has been demonstrated (33), other studies show a decrease in insulin sensitivity, an increase in insulin secretion, an increase in incidence of impaired glucose tolerance and an increase insulin resistance compared to matched controls (56, 57). In accordance to the latter, some studies
show that patients treated for CP have an increased risk for type 2 diabetes mellitus (T2DM) (19, 20, 58-60). This high prevalence of metabolic syndrome, T2DM, dyslipidaemia and obesity contributes to the high cardiovascular and cerebrovascular morbidity and mortality seen in these patients (19, 22, 28, 58-61).

Above all, the quality of life in craniopharyngioma patients is determined by the severity of the excessive weight gain (13). This highlights the importance of sufficient weight and metabolic control and the need of HyOb interventions.

3. Treatment of hypothalamic obesity

3.1. Conservative treatment

Disturbance of appetite regulation, decrease in central sympathetic output and possible diminished energy expenditure could explain the fact that hypothalamic obesity in craniopharyngioma patients is often insensitive for conservative treatment such as diet and exercise (62).

Targeted pharmaceutical options for treatment of HyOb show mixed results. Based on impairment of sympatho-adrenal activation, treating HyOb with a sympathomimetic drug has been suggested. While dextroamphetamine achieves weight stabilization due to improved activity (44), other sympathomimetic drugs such as sibutramine are withdrawn from the market due to unacceptable cardiovascular side effects (63, 64), and while melatonin substitution improves daytime sleepiness and physical activity, it does not clearly impact BMI (65). Management of the parasympathetic dysregulation has been investigated as well. Octreotide, a somatostatin analogue, appears to reduce the amount of weight gain by reducing the insulin secretion hypothesised to contribute to HyOb. However, in some patients only weight stabilization is observed and the analogue is not useful for patients already displaying T2DM as it could impair glycaemic control (46, 47). Combination therapy including diazoxide to decrease insulin secretion and metformin to enhance insulin action in children with HyOb secondary to CP treatment, shows a reduced weight gain, but significant side effects (66). Thus, it can be concluded that pharmaceutical options are tepid at best.

3.2. Bariatric surgery

Bariatric surgery has proven to be highly effective in common obesity (67), with a reduction in overall mortality compared to conservative treatment in matched obese controls (68). As HyOb is a frequently observed morbidity in patients treated for CP and only modest results of weight
control through lifestyle modification and pharmacotherapy have been achieved, other options to treat HyOb such as bariatric surgery could be plausible. However, literature reporting the efficacy of bariatric surgery in HyOb remain scarce. To date, literature on bariatric surgery in HyOb related to a craniopharyngioma is mostly limited to a few case reports and series. A literature search using the terms ‘craniopharyngioma’ and ‘bariatric surgery’ in Embase and Pubmed yielded 14 articles with a total of 39 cases (69-82).

In an attempt to increase research concerning HyOb and to improve its management, the International Registry for Hypothalamic Disorders (www.IRHOD.org) was established. This web-based registry was created to collect participant-reported characteristics of HyOb from patients affected by this rare disease. Craniopharyngioma was reported to be the underlying cause of HyOb in 62% of the patients. Of all treatment options, bariatric surgery performed in 8% of the 87 participants, was associated with the largest weight loss (83).

### 3.2.1. Bariatric procedures

Bariatric surgery aims to reduce weight and maintain weight loss through restriction, malabsorption or a combination of both by adjusting the anatomy of the gastrointestinal tract. Altering the stomach by creating a smaller gastric reservoir with a narrow way out to delay passage of food, causes restriction of food intake, while malabsorption is due to exclusion of parts of the small intestine to decrease the possibility of nutrient absorption (84, 85). Several surgical techniques have been developed including adjustable gastric banding (AGB), Roux-en-Y gastric bypass (RYGB), sleeve gastrectomy (SG) and biliopancreatic diversion without (BPD) or with duodenal switch (BPD-DS). Sleeve gastrectomy has increased in popularity and together with RYGB it accounts for the most commonly performed procedures (86). In the Swedish Obese Subjects (SOS) trial - a large, prospective, controlled intervention study - percentage of total bodyweight loss since baseline reaches its maximum of approximately 38% 1 year after RYGB with some regain thereafter before it stabilizes at 8 to 10 years with a 25% weight loss at 10 years after gastric bypass surgery. On the contrary, the average weight change in matched non-surgically treated obese patients remains ±3% (87). A recent randomized controlled trial with a 5-year follow-up period shows no significant differences in percentage excess BMI loss for sleeve gastrectomy compared to bypass surgery at any point after surgery. However, post hoc analyses comparing percentage of total bodyweight loss since baseline, show a small difference at 5 years (25,0% for SG vs. 28,6% for bypass) (88). Similarly, a second randomized controlled trial with a 5-year follow-up period reports a higher percentage of excess weight loss after gastric bypass compared to sleeve gastrectomy with differences increasing with time. However, at the 5-year mark, the difference is not statistically significant (89). On the contrary, other studies have shown significant differences between
both procedures. In a recent retrospective cohort study, weight loss 1 year after surgery was 30.9% for bypass surgery vs. 23.4% for SG and weight loss 4 years after surgery was 27.5% for bypass surgery vs. 17.8% for SG. The nonconformity in differences between both procedures is likely due to different surgical techniques, different characteristics of participants and a different study design (90).

RYGB, often performed laparoscopically, is based on restriction and malabsorption. First, a small pouch of the upper part of the stomach is created using surgical staples to induce restriction of food intake. Secondly, the small intestine is divided and a gastrojejunostomy is created, connecting the pouch to the mid-jejunum which results in the construction of the alimentary limb, also known as the Roux limb. The continuity of the bowel is restored by a jejuno-jejunal anastomosis between the excluded biliopancreatic limb – the proximal part of the divided small intestine – and the alimentary limb 75-150 cm distally to the gastroenterostomy. Only in the common channel – the segment below the enteroenterostomy - food comes into contact with pancreatic and biliary secretions creating decreased absorption (Fig. 2) (84, 85).

Figure 2 Roux-en-Y gastric bypass procedure
(DeMaria et al., page 2179 (84))
Initially the first stage of a two-stage procedure – SG followed by BPD – sleeve gastrectomy has increased in popularity as a single-stage procedure due to its simplicity and good clinical outcomes. The procedure, also often performed laparoscopically, leaves a narrow tube as alimentary conduit by excision of 70-80% of the lateral stomach causing reduction of the stomach reservoir and therefore restriction of food intake (Fig. 3) (84, 85).

Figure 3 Sleeve gastrectomy procedure
(DeMaria et al., page 2179 (84))

Besides restriction and exclusion of part of the intestine, different mechanisms have been proposed to contribute to the efficacy of bariatric surgery. Alterations of eating behaviour with a decrease in hunger, an increase in satiety and altered food preferences due to a change in food reward or due to dumping syndrome, could contribute to the efficacy of surgery. In addition, alteration of bile acids and gut microbiota, and a possible factor of malabsorption after RYGB depending on the length of the common channel are also proposed mechanisms. Furthermore, a change in energy expenditure, a possible change in vagal afferent signalling through which gut hormones partly exert their effect as well as altered levels of gut hormones such as ghrelin, PYY, glucagon-like peptide-1 (GLP-1), cholecystokinin (CKK) and leptin are suggested (85).

Plasma levels of the orexigenic hormone ghrelin normally increase shortly before every meal and decrease shortly after every meal consistent with the urge to eat (39). In gastric bypass patients however, there is a possibility of suppressed ghrelin levels or an absence of an increase in ghrelin levels seen in diet-induced weight loss, which is consistent with the observed decrease in hunger after RYGB. Therefore, this might contribute to the effect of weight loss after surgery (91-93). However, results of RYGB and ghrelin levels are inconsistent (94). Enhanced secretion of other gastro-intestinal hormones such as PYY and GLP-1, could contribute to surgical weight loss as well. The exaggerated response of PYY to nutrients leads to an increase in satiety due to its effect on the ARC, as well as a delay of gastric emptying...
and an increase in energy expenditure (38, 93, 95-97). Furthermore, GLP-1 – an incretin which promotes postprandial insulin release and inhibits glucagon secretion and is produced by the same entero-endocrine L-cells producing PYY – shows a postprandial increase after RYGB. This further adds to the increase in satiety as it has been reported to inhibit food intake in humans next to slowing gastric emptying (95-100).

Although sleeve gastrectomy is seen as a restrictive option for treatment of obesity, similar hormonal changes including a decrease in fasting and postprandial ghrelin, increase in fasting and postprandial PYY levels and an increase in postprandial GLP-1 levels, indicate that its effectivity is not only due to restriction of food intake (97, 101).

3.2.2. Effect of bariatric surgery on obesity-related health consequences

While the success of bariatric surgery is often expressed by the amount of weight loss achieved, bariatric surgery is also known to have metabolic effects. Remission rate of diabetes mellitus after gastric bypass is reported to be up to approximately 80% with most recent randomized controlled trials reporting similar rates of remission in RYGB as in SG (67, 89, 102-104). However, results depend on the definition of remission, the number of patients included and the term of follow-up. In the SOS trial, remission rate at 2 years after surgery is 72%, while only 36% have remission at 10 years (87). Bariatric surgery compared to intensive medical therapy is associated with a superior and sustained glycaemic control — that is a superior reduction in fasting plasma glucose and glycated haemoglobin (HbA1c) — and a reduction of dependency of oral antidiabetic treatment and insulin (105, 106). The improvement of glycaemic control can be attributed to the exaggerated postprandial GLP-1 secretion seen in RYGB and SG which not only provides an anorexigenic response, but also contributes to an improved β-cell function. Further, improvement of total insulin sensitivity and glucose tolerance is achieved by caloric restriction, which depletes liver fat and increases hepatic insulin sensitivity, and on a long-term basis weight loss, which improves peripheral muscle insulin sensitivity (107). In addition, an improvement after bariatric surgery of other cardiovascular risk factors such as hyperlipidaemia and AHT allowing a decrease in lipid-lowering therapy and antihypertensive medication, as well as an improvement of obstructive sleep apnoea (OSA) is observed (67, 87, 106).

The significant and sustainable change in bodyweight, improvement in cardiovascular risk factors, as well as a decrease in cardiovascular events and deaths seen in obese adults after bariatric surgery (108), demonstrate the many benefits bariatric surgery can provide. However, it should also be taken into consideration that perioperative and postoperative complications and mortality – although relatively uncommon – have been observed (84).
3.2.3. Hormone replacement therapy

It has been shown that craniopharyngioma as an underlying cause of hypopituitarism is associated with a significantly high standard mortality ratio (17). This reiterates the importance of the life-long hormone substitution therapy in patients treated for CP with pituitary hormone deficiencies. Growth hormone deficiency could partly be responsible for the metabolic derangements such as dyslipidaemia contributing to the high cardiovascular mortality in patients with hypopituitarism (17, 109). Although GH replacement therapy could reduce insulin sensitivity, it can be beneficial to lipid profile and body composition as it increases lean body mass and decreases body fat mass (110). Furthermore, adequate replacement for hypothyroidism could have beneficial effects on bodyweight and lipid levels and testosterone replacement therapy has been shown to improve body composition and glucose homeostasis as well (111-113). Over- or undertreatment of some of the pituitary hormone deficiencies could therefore negatively influence bodyweight and metabolic status. Excess glucocorticoid dosing for example, could cause significant weight gain and impaired glucose metabolism, as a glucocorticoid dose response relation with BMI, TG levels, total cholesterol levels, LDL levels and HbA1c levels in patients with hypopituitarism has been observed (114). However, undertreatment could lead to an acute adrenal insufficiency. Therefore, close monitoring of variations in the hormone replacement therapy in patients with HyOb is essential.

Although bariatric surgery could be proposed as a therapeutic option in patients with CP-related HyOb, it is important to consider the effects of bariatric surgery on endocrine hormone substitution therapy.

Pharmacokinetics and -dynamics, which differ in obese and lean subjects (115), may change following weight loss, therefore resulting in alteration of drug requirements. Furthermore, a decrease of oral drug absorption post-bariatric surgery might lead to acute adrenal insufficiency or severe hypothyroidism. In bariatric procedures involving some type of gastric restriction, a decrease in oral drug absorption could be attributed to mechanisms such as reduced drug disintegration due to a decrease of gastric mixing, altered drug dissolution and solubility due to an increase of pH in the newly formed stomach and a reduced absorption rate due to reduced gastric emptying. Clearly, procedures with a malabsorption component, have more potential to induce drug malabsorption due to reduction in intestinal transit, intestinal length and mucosal contact, and contact with bile acids, of essence in high lipophilic drugs such as levothyroxine, which is restricted to the common channel. Lipophilic drugs also rely on enterohepatic circulation which is one of the two main risk factors for reduced absorption next to poorly intrinsic absorptive capacity of the drug. Lastly, depending on the drug and surgery type, bypassing specific regions of the small intestine could influence drug metabolism and
efflux (116).
However, there is little information on specific medications and its absorption after bariatric surgery which limits the possibility of recommendations on what changes in dosing after surgery should be made. Also, the effect of bariatric surgery on hormone substitution therapy in patients treated for HyOb after CP treatment has only been addressed in a few previous studies with only one study specifically investigating the absorption of hormone replacement therapy (76, 77, 82). It is therefore imperative to monitor patients for efficacy and safety of drugs after bariatric surgery.
4. Research question and objectives

It could be hypothesised that the efficacy of bariatric surgery depends, at least partly, on intact hypothalamic function as for example gut hormones partly exert their effects on hypothalamic nuclei (36-38). Furthermore, a disturbed appetite and decreased energy expenditure reported in patients treated for CP (32, 41, 42), could interfere with post-bariatric diet restrictions and requested lifestyle modification such as daily activity to ameliorate the effect of the procedure. Also, in terms of safety, bariatric surgery could interfere with drug absorption (116). As studies on the efficacy and safety of bariatric surgery for craniopharyngioma-related hypothalamic obesity remain scarce, this study aims to research the following questions:

- is bariatric surgery, proven to be effective in common obesity (67), effective in patients with hypothalamic obesity secondary to craniopharyngioma treatment in terms of weight loss and improvement or remission of T2DM, hyperlipidaemia, AHT and OSA; and,
- is bariatric surgery a save therapeutic option in terms of its effect on pituitary hormone substitution therapy in patients suffering from HyOb and hypopituitarism following craniopharyngioma therapy?

In order to do so, weight loss after sleeve gastrectomy and Roux-en-Y gastric bypass in patients treated for craniopharyngioma and in matched control subjects with non-hypothalamic obesity during a 2-year follow-up is investigated. In addition, improvement or remission of comorbidities associated with obesity including type 2 diabetes mellitus, hyperlipidaemia, hypertension and obstructive sleep apnoea in patients with hypothalamic obesity after bariatric surgery is researched. Secondly, alterations of hormone replacement therapy for pituitary hormone deficiencies in patients treated for craniopharyngioma after bariatric surgery is documented.

Contribution of the student

Patients treated for CP and receiving bariatric surgery for HyOb were gathered by the supervisors Prof. Dr. Y. Van Nieuwenhove and Prof. Dr. B. Lapauw and a matched case-control design was proposed. Matching variables were determined by the student and the matching process was performed in cooperation with Prof. Dr. Y. Van Nieuwenhove. The student requested ethical approval in cooperation with the study nurses at the department of Gastrointestinal Surgery of Ghent University Hospital, and drew up an informed consent which was sent to the selected patients. Subsequently, the student performed data extraction from electronic patient files, data analyses, interpreted the data and made conclusions.
Materials and methodology

1. Study design

In this retrospective matched case–control study, five eligible patients could be identified by a computer-based search in a database based on electronic patient files which included over a 1000 patient records and data of patients who underwent bariatric surgery from September 2007 to August 2017 at the department of Gastrointestinal Surgery at Ghent University Hospital, a tertiary care centre. Inclusion criteria were hypopituitarism and bariatric surgery as treatment for obesity secondary to treatment of a craniopharyngioma; this ensures that the obesity is caused by hypothalamic impairment (cf. Results – Fig. 5). In all five patients, diagnosis of craniopharyngioma was based on MRI and/or CT and confirmed by pathology. Pituitary hormone deficiencies were diagnosed using pituitary function testing, information of neurosurgical removal of the pituitary stalk and/or gland or laboratory parameters. Patients were surgically treated for hypothalamic obesity between 2013 and 2016 by sleeve gastrectomy or Roux-en-Y gastric bypass; no previous bariatric procedures had been performed.

Patients treated for a craniopharyngioma were individually matched to 2 control subjects; patients derived from the abovementioned database of the department of Gastrointestinal Surgery without any kind of hypothalamic dysfunction. Each patient treated for CP was individually matched to its two optimal control patients, precisely with respect to gender and bariatric procedure (sleeve gastrectomy or Roux-en-Y gastric bypass), and as narrow as possible with respect to age at bariatric procedure, preoperative BMI and date of bariatric surgery as these clinical factors might affect the weight loss response after surgery. Individual matching was performed using a Filemaker database which included the abovementioned matching variables of both CP and control patients. If selected control patients had hypothalamic dysfunction (N=1), previous bariatric procedures (N=3), lack of postoperative data concerning bodyweight (N=3), and a non-limited list of disorders and drugs which may influence metabolic profile and bodyweight including thyroid disorders, corticoid use… (N=2), they were excluded and replaced by the following most optimal matched patient (cf. Appendix 1 – Fig. 4). All patients fulfilled the medical criteria in order to receive reimbursement by the Belgian authorities (age above 18 years, BMI > 40 kg/m² or 35 kg/m² if diabetes, hypertension treated with three antihypertensive drugs, sleep apnoea or failure of previous bariatric procedure and unsuccessful conservative treatment) and had stable bodyweight for at least three months prior to the bariatric procedure. Bariatric surgery in selected control patients was performed between 2010 and 2015.
All patients were chronically monitored at the departments of Endocrinology and/or Gastrointestinal Surgery. Data from the electronic patient files of the patients included was extracted in 2017-2018. Patients were asked to participate by an informed consent. All selected patients except one control patient participated. The control patient was replaced by the following most optimal matched patient. The protocol of this study was reviewed and ethical approval was obtained from the Ethics committee of Ghent University Hospital, Belgium.

2. Patient characteristics

Data on craniopharyngioma treatment, recurrence of tumour, tumour- and/or treatment related complications and morbidity, bariatric surgery and presence of comorbidities at baseline (baseline is defined as evaluation at bariatric surgery) were collected from the electronic patient files. Resection of the tumour was either complete or incomplete based on the surgeon’s assessment of the degree of resection and the presence of residual tumour evaluated on postoperative imaging including MRI or CT which confirmed complete resection in case of no residual tumour. Tumour recurrence was defined as reappearance or regrowth of the tumour on imaging with or without associated symptoms more than 6 months after initial therapy and time to recurrence was calculated from the date of initial treatment. Tumour- and/or treatment related complications and morbidity including pituitary hormone deficits were retrieved from patient files. Data concerning age and anthropometric characteristics including bodyweight and -height at CP treatment, at bariatric surgery and two years after bariatric surgery were analysed and body mass index (kg/m²) was calculated. Time to bariatric surgery was calculated from the date of initial craniopharyngioma therapy and the presence of comorbidities including T2DM, IGT, hyperlipidaemia, AHT and OSA at baseline were evaluated (cf 4.2.).

3. Bariatric procedure

All patients were evaluated by a multidisciplinary team (bariatric surgeon, endocrinologist, nutritionist and psychologist) to be eligible for bariatric surgery and underwent routine preoperative assessment.
All surgical procedures were conducted laparoscopically and operation techniques were standardised and performed as follows:

- sleeve gastrectomy consisted of division of the antrum 6 cm away from pylorus and the gastric sleeve was created using a 34 Fr bougie,
- Roux-en-Y gastric bypass consisted of creation of a small pouch that was divided from the proximal lesser curvature of the stomach after dissecting the angle of His. A manual gastrojejunostomy was made by an anastomosis between the pouch and a Roux limb of jejunum created by the division of the jejunum 70 cm distal to the ligament of Treitz. The biliopancreatic limb was semi-mechanically anastomosed to the jejunum 100 cm distally creating an enteroenterostomy.

Data concerning early postoperative complications defined as within 30 days after bariatric surgery, and late complications defined as more than 30 days after surgery, were collected from the electronic patient files.

4. Outcomes of interest

4.1. Bodyweight change

To evaluate weight change caused by the tumour and its treatment, bodyweight was collected from the electronic patient files of patients treated for CP at CP treatment and every year thereafter up to the date of bariatric surgery. Weight gain was calculated at each year after CP treatment as percent of total bodyweight gained since CP treatment.

To compare weight loss between patients with HyOb related to a craniopharyngioma and control subjects with non-hypothalamic obesity, bodyweight at bariatric surgery, at 3 months and 6 months after bariatric surgery (with a range of 2 months), and at 12 and 24 months after the bariatric procedure (with a range of 4 months) in both patients treated for craniopharyngioma and control patients was retrieved from electronic patient files. Weight loss at each postoperative evaluation was calculated as percent of total bodyweight lost since bariatric surgery (%TWL).

4.2. Obesity-related comorbidities

Presence of comorbidities (T2DM, IGT, hyperlipidaemia, AHT and OSA) at baseline, 12 months and 24 months after bariatric surgery was retrieved from the electronic patient files of patients treated for CP.

The diagnosis of T2DM and IGT was based on standard criteria of the American Diabetes
Association. Diagnosis of T2DM was based on fasting plasma glucose (≥ 126 mg/dL), 2-h plasma glucose during a 75-g oral glucose tolerance test (OGTT) (≥ 200 mg/dL), HbA1c (≥ 6.5%), random plasma glucose in a patient with classic symptoms of hyperglycaemic or hyperglycaemic crisis (≥200 mg/dL) or treatment with oral hypoglycaemic agents or insulin. Diagnosis of IGT was based on 2-h plasma glucose levels during a 75-g OGTT (140-199 mg/dL) (117). The date of diagnosis of T2DM was collected to evaluate the duration of the condition from diagnosis up to bariatric surgery. Diagnosis of hyperlipidaemia was defined according to the NCEP ATP-III guidelines (Adult Treatment Panel III report of the National Cholesterol Education Program) as total cholesterol ≥ 200 mg/dL, LDL-cholesterol ≥ 130 mg/dL (for moderate risk patients), HDL-cholesterol ≤ 40 mg/dL or triglycerides ≥ 150 mg/dL (118), or based on the use of lipid-lowering medication. Diagnosis of arterial hypertension was based on guidelines of the European Society of Cardiology (ESC) and the European Society of Hypertension (ESH), according to whom the definition of AHT can be described as follows: office systolic blood pressure values of ≥140 mmHg and/or diastolic blood pressure values of ≥90 mmHg (119), or treatment with antihypertensive medication. Lastly, diagnosis of OSA was based on polysomnographic reports.

Remission of comorbidities was evaluated at 12 and 24 months after bariatric surgery. Remission of T2DM could be either partial or complete. Partial remission was defined as HbA1c not diagnostic for T2DM (< 6.5%), fasting plasma glucose between 100-125 mg/dL for at least one year and absence of pharmacologic therapy or ongoing procedures. Complete remission was defined as normal glucose parameters (HbA1c < 6.0%), fasting plasma glucose < 100 mg/dL for at least one year and absence of pharmacologic therapy or ongoing procedures (120).

Remission of hyperlipidaemia was defined as a return of normal lipid values without medication use.

To evaluate remission, the abovementioned laboratory parameters at bariatric surgery and 12 and 24 months after bariatric surgery as well as pharmacological treatment used at 12 and 24 months after bariatric surgery compared to baseline were collected from the electronic patient files of patients treated with CP and diagnosed with the corresponding condition (T2DM or hyperlipidaemia). Medication was reported according to the therapeutic classes mentioned in the Belgian Centre for Pharmacotherapeutic Information (BCFI/CBIP) (121).

Remission of OSA after bariatric surgery could not be evaluated due to the lack of polysomnographic parameters as a polysomnography is not standardised after bariatric surgery. However, subjective improvement of OSA based on documented improvement in
sleep hygiene and symptoms of sleep apnoea and based on self-discontinuation of the use of a nasal continuous positive airway pressure (nCPAP) device due to improved symptoms, was retrieved from electronic patient files.

Information concerning remission of AHT based on systolic and diastolic blood pressure and use of antihypertensive treatment was not retrieved from patient files as no patients treated for craniopharyngioma were diagnosed with hypertension before or after bariatric surgery.

4.3. Hormone replacement therapy

In all patients treated for craniopharyngioma, hypopituitarism was managed with hormone replacement therapy using oral hydrocortisone and levothyroxine, subcutaneous GH, oral or nasal desmopressin and oral sex steroids in case of oestrogen/progestin deficiency or intramuscular sex steroids in case of testosterone deficiency. Doses of hormone replacement therapy at bariatric surgery and 6, 12 and 24 months after the bariatric procedure were retrieved from the electronic patient files of patients treated for CP. Postoperative alterations - based on the decision of the treating physician - of pituitary hormone replacement therapy initiated before bariatric surgery, were investigated. Alterations of hydrocortisone dose were based on signs and symptoms of adrenal insufficiency. Incidence of adrenal crises was analysed. Alterations in oestrogen/progestin dose and testosterone dose were based on symptoms of hormone deficiency. Alterations in recombinant human growth hormone dose were made to keep serum insulin-like growth factor I levels within the age- and sex-adjusted reference range. Alterations in levothyroxine dose were made to keep serum free thyroxine levels (fT3,fT4) within the reference range and alterations in desmopressin dose were based on fluid balance (normal diuresis), plasma and urinary osmolality and electrolytes levels.

5. Statistical analysis

The Statistical Package for Social Sciences (SPSS 25, Chicago, IL, USA), was used to conduct statistical analyses. Characteristics of patients were described as median and range in case of continuous data because of small sample size. Categorical data were described as observed frequencies and percentages. Comparison of categorical baseline characteristics between patients treated for craniopharyngioma and control subjects was performed using the Fisher’s Exact test as requirements for Chi-square test were not met. In case of numerical baseline characteristics, the non-parametric Mann–Whitney U-test was chosen as sample sizes were small.
Because of the matched case-control design inducing dependent variables, and the use of longitudinal data, comparison of weight loss at 3, 6, 12 and 24 months after bariatric surgery to baseline between patients treated for craniopharyngioma and control patients was performed by using a linear mixed model. A linear mixed model for percentage weight loss since baseline was fitted with random intercepts for patient treated for CP and for their matching cluster (the two matched control patients), and with period of follow-up (categorical) and interaction between period of follow-up and group (case-control) as fixed factors. A linear mixed model with period of follow-up as a continuous variable had a higher Akaike’s information criterion (AIC) and was therefore a worse model fit compared to the chosen linear mixed model including period of follow-up as a categorical variable. By excluding a main effect for group, we assumed no difference in mean weight loss at baseline between cases and controls. Missing values in the outcome are assumed to be missing at random: missingness can be dependent on group and period of follow-up, but not on other unobserved variables.

Statistical significance was considered as p<0.05. All reported p-values were tested two-sided.

To compare both bariatric procedures, an algorithm including an additional interaction between group and surgical procedure (sleeve gastrectomy or Roux-en-Y gastric bypass) was necessary, however this algorithm was not able to fit the limited sample data. Therefore, individual data of each patient were reported for both procedures separately.
Results

1. Patient characteristics

All five eligible patients (4 women) with bariatric surgery for hypothalamic obesity after craniopharyngioma treatment were included in this study. Characteristics of patients are shown in Table 1 (cf. Appendix 1).

Median age at CP treatment was 28 years (range [12;37]) and median BMI at craniopharyngioma treatment was 30.4 kg/m² (range [19.9;37.0]). Age at CP treatment resembled age at diagnosis of CP. However, one patient (case 5) was misdiagnosed with prolactinoma for 11 years. In one case tumour reoccurred after 19 years. In this patient, only bodyweight at treatment of tumour recurrence was available. The tumour was treated with resection and/or punction of the cystic component and postoperative radiotherapy was added if resection was incomplete. One case (case 5) developed hydrocephalus after treatment of craniopharyngioma due to obstruction, which was treated with a ventriculostomy. In another patient (case 1), treatment of craniopharyngioma was followed by a cerebrovascular accident which further led to neurocognitive disorder and long-term revalidation. During the follow-up period, the patient was not able to return to his pre-illness status concerning employment. All patients developed panhypopituitarism with diabetes insipidus.

Subsequently, all patients developed severe obesity for which bariatric surgery was performed a median 10 years (range [1;26]) after craniopharyngioma treatment. Three patients who had treatment for craniopharyngioma received a Roux-en-Y gastric bypass, in two patients sleeve gastrectomy was performed. Median age at bariatric surgery was 38 years (range [27;47]) and median BMI at bariatric surgery was 41.3 kg/m² (range [37.9;46.3]). Eventually, median BMI two years after bariatric surgery was 34.9 kg/m² (range [24.3;51.9]). Comorbidities at baseline were T2DM, IGT and OSA. No patient was diagnosed with AHT.
Table 2
Baseline characteristics of patients with hypothalamic obesity versus patients with non-hypothalamic obesity

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>CP</th>
<th>Control</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>5</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male N (%)</td>
<td>1 (20)</td>
<td>2 (20)</td>
<td>NS</td>
</tr>
<tr>
<td>Female N (%)</td>
<td>4 (80)</td>
<td>8 (80)</td>
<td></td>
</tr>
<tr>
<td><strong>Bariatric surgery</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SG N (%)</td>
<td>2 (40)</td>
<td>4 (40)</td>
<td>NS</td>
</tr>
<tr>
<td>RYGB N (%)</td>
<td>3 (60)</td>
<td>6 (60)</td>
<td></td>
</tr>
<tr>
<td><strong>Median age (years) at BS [range]</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BS</td>
<td>38 [27;47]</td>
<td>43 [30;46]</td>
<td>NS</td>
</tr>
<tr>
<td>SG</td>
<td>34 [27;40]</td>
<td>34 [30;45]</td>
<td>NS</td>
</tr>
<tr>
<td>RYGB</td>
<td>38 [36;47]</td>
<td>45 [38;46]</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Median BMI (kg/m²) at BS [range]</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BS</td>
<td>41,3 [37,9;46,3]</td>
<td>41,1 [38,9;48,1]</td>
<td>NS</td>
</tr>
<tr>
<td>SG</td>
<td>40,6 [37,9;43,2]</td>
<td>41,0 [38,9;44,4]</td>
<td>NS</td>
</tr>
<tr>
<td>RYGB</td>
<td>41,3 [40,1;46,3]</td>
<td>41,1 [40,6;48,1]</td>
<td>NS</td>
</tr>
</tbody>
</table>

Abbreviations: N, number; CP, patient treated for craniopharyngioma; BS, bariatric surgery; SG, sleeve gastrectomy; RYGB, Roux-en-Y gastric bypass; NS, not significant

Table 2 represents baseline characteristics of patients with hypothalamic obesity due to craniopharyngioma treatment compared to patients with non-hypothalamic obesity. Matching resulted in two groups that were not significantly different with respect to gender, type of bariatric surgery, age at bariatric surgery and BMI at bariatric surgery.
2. Bodyweight change after craniopharyngioma treatment

Percentage of total bodyweight gained since CP treatment each year after CP treatment until bariatric surgery is given in Figure 5.

![Weight change after craniopharyngioma treatment](image)

Figure 5. Weight change after craniopharyngioma treatment until bariatric surgery

Weight change is given in percent of total bodyweight changed since CP treatment and is reported until bariatric surgery. Individual data are presented. Abbreviations: CP, date of initial craniopharyngioma treatment with exception of case 4 in whom CP represents date of treatment of tumour recurrence as bodyweight was only available after treatment of the reoccurred tumour.

In all patients, maximum change in bodyweight after CP treatment was observed during the first year after craniopharyngioma therapy (median 29.9%; range [16.7;78.0]).

3. Bodyweight change after bariatric surgery

3.1. Linear mixed model

By using a linear mixed model analysis, estimated mean weight loss and estimated mean weight difference at 3, 6, 12 and 24 months after bariatric surgery compared to baseline between patients treated for a craniopharyngioma and control patients was calculated (Fig. 6).
Figure 6. Weight change after bariatric surgery in patients with hypothalamic obesity after craniopharyngioma treatment and in patients with non-hypothalamic obesity

Data are presented as estimated mean weight loss at 3, 6, 12 and 24 months after bariatric surgery compared to baseline in 5 patients treated for craniopharyngioma (blue) and 10 control patients (red), both treated similarly with sleeve gastrectomy or Roux-en-Y gastric bypass. Weight change is given as %TWL. Missing’s were accounted for and were dependent on group and period of follow-up. Coloured ** represents p<0,01 for estimated mean weight loss compared to baseline in patients treated for craniopharyngioma and control patients. Black * represents p<0,05 for mean difference in weight loss compared to baseline between both groups. Numerical data of estimated mean weight loss and mean weight difference with 95% CI are given underneath.

Abbreviations: CP, craniopharyngioma; CI, confidence interval; SG, sleeve gastrectomy; RYGB, Roux-en-Y gastric bypass; BS, at bariatric surgery
An exponential decrease of estimated mean weight loss in patients treated for craniopharyngioma is visualized with a maximal mean weight loss at 6 months of follow-up, followed by a weight rebound with a mean weight loss of 14.7% at 2 years of follow-up. Mean weight loss compared to baseline was significantly different at each postoperative evaluation (p<0.01). In control patients, an exponential decrease of estimated mean weight loss is visualized with its maximum 1 year after bariatric surgery. A weight rebound is followed with an estimated mean weight loss of 28.3% at 2 years of follow-up. Mean weight loss is significantly different compared to baseline at any point after bariatric surgery (p<0.001).

Estimated mean difference in weight loss compared to baseline between craniopharyngioma and control patients, although not significant at 3 and 6 months after bariatric surgery, is significant at both 1 and 2 years after bariatric surgery (p<0.05), with an estimated mean difference between both groups of 13.6% at 2 years of follow-up compared to baseline (p=0.018).
3.2. Observation of bodyweight change after sleeve gastrectomy and Roux-en-Y gastric bypass

As no statistical analysis was possible to compare SG and RYGB between craniopharyngioma and control patients due to the limited amount of data, percent weight change evolved since baseline was observed individually at 3, 6, 12 and 24 months (Fig. 7 and Fig. 8).

![Weight change after sleeve gastrectomy](image)

**Figure 7. Weight change after sleeve gastrectomy in patients with hypothalamic obesity after craniopharyngioma treatment and in patients with non-hypothalamic obesity**

Weight change at 3, 6, 12, and 24 months after sleeve gastrectomy of 2 patients with hypothalamic obesity after treatment for craniopharyngioma (blue) and 4 control patients with non-hypothalamic obesity (red) is given of each patient individually. Patients treated for craniopharyngioma and their matched control patients are presented with the same line pattern. Number of patients included are reported underneath. Weight change is given as %TWL.

CP: craniopharyngioma

Figure 7 represents weight loss after SG in patients treated for craniopharyngioma and control patients. Overall, it can be observed that all control patients lost weight at any point of follow-up compared to baseline in contrary to only one out of two patients treated for craniopharyngioma. Case 1 lost its maximum weight 6 months after sleeve gastrectomy, but regained weight afterwards leading up to a weight gain of 20.0% at 2 years of follow-up compared to baseline. On the contrary, its matched control patient lost 35.8% at 2 years of follow-up. Comparable data for the second matched control patient 2 years after surgery were
not available. The second patient treated for CP lost its maximum weight at 6 months of follow-up, followed by a weight regain with a weight loss of 7.9% at 2 years of follow-up compared to baseline. Its matched control patients lost 10.4%. Comparable data for the other matched control patient 2 years after surgery were not available.

Figure 8. Weight change after Roux-en-Y gastric bypass in patients with hypothalamic obesity after craniopharyngioma treatment and in patients with non-hypothalamic obesity

Weight change at 3, 6, 12, and 24 months after Roux-en-Y gastric bypass of 3 patients with hypothalamic obesity after treatment for craniopharyngioma (blue) and 6 control patients with non-hypothalamic obesity (red) is given of each patient individually. Patients treated for craniopharyngioma and their matched control patients are presented with the same line pattern. Number of patients included are reported underneath. Weight change is given as %TWL.

CP: craniopharyngioma

Figure 8 represents weight loss after RYGB in patients treated for craniopharyngioma and control patients. Overall, it can be observed that both CP and control patients lost weight at any point of follow-up compared to baseline. At 2 years of follow-up, only one CP patient is observed to lose less weight than its matched control patients (21.7% in case 3 vs. 29.0% and 41.9% in control subjects). Observation of weight loss at 2 years of follow-up in the two other patients treated for CP shows a slightly greater weight loss in patients treated for CP compared to its matched controls (24.7% in case 4 vs. 22.4% and 22.7% in control subjects / 39.5% in case 5 vs. 33.6% and 35.3% in control subjects).
3.3. Complications

The most common complications were abdominal pain, vomiting and diarrhoea. No major differences between both groups were present.

One case (case 3) experienced early complications including epigastric pain and vomiting. Technical investigations excluded any underlying cause of stenosis. Complaints were resolved and no late complications were present. In control patients vomiting as an early complication and mild diarrhoea and abdominal pain as a late complication were present. Relevant underlying causes including stenosis were absent.

Revisional surgery was not needed in any patient. No major complications were reported.

4. Obesity-related comorbidities

4.1. T2DM and IGT

At baseline, presence of T2DM was observed in two patients, as to one patient in whom IGT was noted.

Both diabetic patients received metformin, and long- and ultrafast-acting insulin at baseline. Case 2 was diagnosed with T2DM eleven years before bariatric surgery, compared to less than 1 year before surgery in case 3.

Case 2 was able to replace the insulin therapy for a gliclazide one year after sleeve gastrectomy and HbA1c declined from 9.6% to 6.2% with a weight loss of 11.4% compared to baseline. However, 2 years after bariatric surgery with a weight loss of 7.9% compared to baseline, while treatment did not change, HbA1c increased up to 9.1%. Thus, it can be concluded that neither partial nor complete remission was present in this patient.

However, in the second diabetic patient (case 3) who lost 20.3% at 1 year of follow-up and 21.7% at 2 years of follow-up, observation was made that treatment had entirely been stopped at both 1 and 2 years after RYGB with a decline of HbA1c from 6.3% at baseline to 5.6% after one year which remained stable the second year after bariatric surgery. Fasting plasma glucose remained under 100 mg/dL during the entire period of follow-up, therefore it could be concluded that a complete remission of T2DM was present.

Although we were not able to report a remission of IGT to normal glucose tolerance due to unavailability of OGTT data, the patient (case 4) who lost 26.0% and 24.7% at respectively 1 and 2 years of follow-up of its weight, was able to quit metformin taken at baseline during both years of follow-up after RYGB with a stable HbA1c of 5.0%.
Case 1, in whom a weight gain of 20.0% 2 years after sleeve gastrectomy was reported, was newly diagnosed with T2DM (HbA1c 8.8%) at 2 years of follow-up for which antidiabetic medication (metformin, gliclazide and GLP-1 analogues) was started.

4.2. Hyperlipidaemia

Hypertriglyceridemia at baseline was observed in one patient (case 2) and treated with fenofibrate. The treatment continued after bariatric surgery during the entire 2-year follow-up period. The triglycerides levels decreased from 705 mg/dL to 220 mg/dL one year after sleeve gastrectomy. However, after 2 years the levels increased up to 402 mg/dL in spite of treatment of fibrate which could lead to the observation of absence of remission.

4.3. OSA

OSA was diagnosed in three patients with HyOb treated for craniopharyngioma. Due to lack of polysomnographic results and lack of data on subjective improvement after bariatric surgery, remission or improvement of OSA could not be evaluated. One patient met the criteria for the use of nCPAP. The use of nCPAP after bariatric surgery was discontinued after 1 year. However, the self-discontinuation was due to discomfort rather than improvement.

5. Hormone replacement therapy

Table 3 (cf. Appendix 1) shows dosage of individual hormone replacement therapy in patients treated for craniopharyngioma at baseline and 6, 12 and 24 months after bariatric surgery. All patients received hormone replacement therapy for pituitary hormone insufficiency, although two patients did not receive growth hormone replacement therapy. Dosage of hydrocortisone only slightly decreased in one patient 6 months after bariatric surgery. In all other patients, dosage remained unchanged. No adrenal crises were mentioned in patient reports. Dosage of levothyroxine increased in 3 patients after 1 and 2 years. In one patient the dosage decreased after two years. No adjustments in the preparation of oestrogen-progestin in the female craniopharyngioma patients were necessary. In the only male patient, dosage of testosterone replacement therapy increased after 1 year. Only one patient needed a slight decrease in growth hormone replacement after 1 year. In two patients desmopressin was reduced after 2 years, in one patient it was increased. One patient changed from a nasal route of administration to desmopressin per os after 6 months.
Discussion

Craniopharyngioma and its treatment leading to significant weight gain and multiple pituitary hormone deficiencies, are associated with increased morbidity and mortality (17, 59). As hypothalamic obesity appears to be resistant to conservative treatment (62), bariatric surgery could be a therapeutic option. However, the possibility of hypothalamic damage and affected drug absorption after surgery interfering with pituitary hormone replacement therapy, question the efficacy and safety of bariatric surgery as a treatment modality. As there has only been a limited amount of cases described in literature, this matched case-control study further adds data on the efficacy of bariatric surgery as treatment for CP-related HyOb.

1. Patient characteristics

This study included five patients treated for craniopharyngioma of whom only one was diagnosed with craniopharyngioma in childhood according to the lower peak (5 - 14 years) of the reported bimodal age distribution (4). The other patients, diagnosed in adulthood, did not match this distribution.

In accordance to literature however, reporting obesity as a presenting symptom, three out of five patients had a BMI $\geq 30$ kg/m$^2$ at presentation which can be attributed to the hypothalamic disturbance of the tumour itself (9, 10, 18).

Subsequently, differences between patients in treatment approaches including extent of tumour removal and use of additional radiotherapy could have been expected as craniopharyngioma treatment is controversial and depends on the adherence of the tumour to hypothalamic tissue (8, 11-15). In two patients in whom radiation doses were mentioned, doses above 51 Gy were reported. Indeed, this has been reported to be a predictive factor for postoperative obesity (40). Furthermore, heterogeneous characteristics in patients concerning residual tumour, tumour recurrence and the necessity of multiple therapies were present. As these treatment characteristics are associated with hypothalamic lesions and significant hypothalamic morbidity including postoperative weight gain (31), differences in intact hypothalamic function between included patients can be speculated.
2. Outcomes of interest

2.1. Bodyweight change

Although bariatric surgery induced a significant estimated mean weight loss at 2 years of follow-up compared to baseline in patients treated for craniopharyngioma, the efficacy of bariatric surgery in terms of weight loss seemed to be superior in patients with non-hypothalamic obesity to patients with HyOb as a significant estimated mean weight difference at 2 years of follow-up compared to baseline between both groups was shown. Furthermore, without drawing any conclusions as the sample size was too limited, it could be observed that in both procedures weight loss in all control patients was reported. However, in patients with HyOb following CP treatment, contrary to all three patients after RYGB, only one out of two patients after SG at 2 years of follow-up lost weight.

Previous results on bariatric surgery in CP-related HyOb are scarce and are mainly based on case reports with differences in population characteristics and heterogeneous reporting of outcomes concerning weight loss, making it difficult to compare data. However, five small case reports and case series observed weight loss after RYGB in all eight cases (71-74, 82). Only one patient demonstrated a pattern of weight regain (82). Although mostly case reports have been published, two other case-control studies compared weight loss in patients with CP-related HyOb to control patients with common obesity. Wijnen et al. performed a retrospective matched case-control study which included five patients treated for CP-related HyOb with RYGB and three with SG versus 75 control patients. Contrary to our results reporting a significant estimated mean weight difference of 13.6% at 2 years of follow-up compared to baseline between CP and control patients, Wijnen et al. showed a mean difference in weight loss of 6% between both groups 2 years after surgery which appeared not to be significant. However, it should be noted that more than 50% of control patients were lost to follow-up. The authors suggested RYGB being an effective therapeutic option for hypothalamic obesity as weight loss was comparable in CP and control patients 2 years after RYGB, but not after SG. A meta-analysis performed in the study, showed similar results one year after bariatric surgery (77). Weismann et al. performed a retrospective non-matched case-control study which included nine patients treated for craniopharyngioma and 143 control patients with common obesity who were significantly older and had more pronounced metabolic disturbances compared to patients treated for CP. Sleeve gastrectomy in four patients treated for CP, contrary to control patients, was not associated with weight loss after a median follow-up of two years. However, similar to control patients, two patients who underwent gastric bypass surgery did lose weight after a median follow-up of three years, although it should be noted
that different procedures were performed as one patient underwent a distal gastric bypass surgery, while the other underwent a standard RYGB procedure (78).

As both case-control studies showed SG to be less efficient, our reported inferior results of surgically induced weight loss in patients treated for CP could be related to an insufficient weight loss after SG. We did observe absence of weight loss after SG at 2 years of follow-up in one out of two patients. However, definite conclusion concerning this assumption cannot be made due to the limited sample size. Above all, although abovementioned studies seemed to show SG to be less effective compared to RYGB, a weight loss percentage of about 20% after both SG and RYGB at one year of follow-up has been shown by a meta-analysis of case series including 8 and 6 cases of CP-related HyOb who underwent respectively SG and RYGB (69).

Furthermore, in a more recent retrospective case series, weight was reduced in all three patients 2 years after SG, although in one patient continuous weight regain occurred after the first 6 months (76). It should also be noted that the weight loss failure after SG in one out of two patients reported in our study could have been influenced by operative complications of hypothalamic surgery performed one year prior to the SG as the neurosurgical procedure was followed by the development of a neurocognitive disorder. Deterioration of neuropsychological and cognitive function has been shown to be related with CP treatment leading to a decrease in independence in performing basic daily activities (8, 10, 18, 19, 25). Indeed, the patient had long-term revalidation after hypothalamic surgery and was not able to return to his pre-illness status concerning employment. This could have been a decisive factor in terms of our reported surgically induced weight loss results in CP-related HyOb as in contrary to all four other included patients, the patient eventually gained weight compared to baseline.

In contrast to SG and gastric bypass surgery, no previous studies report positive results in terms of weight loss after laparoscopic adjustable gastric banding (LAGB). In a retrospective study, four patients with CP who underwent LAGB had weight loss after a short-term follow-up. Even so, despite changes in eating behaviour, after a long-term follow-up LAGB was not associated with weight loss (79, 80). This observation was confirmed by Weismann et al. describing no weight loss, in contrast to control patients, after a long-term follow-up in six CP-related hypothalamic obese patients after LAGB (78). Nevertheless, LAGB was able to stabilize the weight gain rate (78-80). It has been shown that most of the weight gain seen in treated craniopharyngioma patients is observed the first year after craniopharyngioma treatment (30-32). This is in line with our observations as the percentage of weight gain was maximal the first year after CP therapy in all five patients. Although the intention of bariatric surgery is significant weight loss, bariatric surgery performed early after CP treatment could also decelerate or stabilize the weight gain rate seen after hypothalamic surgery which could prevent development of long-term obesity-related morbidities such as T2DM.
Furthermore, although it could be speculated that differences in weight loss after various surgical procedures in patients with CP may be attributed to gut hormones changes as it seems likely to assume that change in gut hormone secretion seen after bariatric surgery in common obesity is also present in HyOb patients, data on this topic are limited and inconsistent. The hypothesis that GLP-1 may contribute to weight loss was assessed by Bretault et al. Increased GLP-1 levels occurred after RYGB, but not after SG. Nevertheless, weight loss and a decrease of insulin resistance were observed in all three patients (70). On the contrary, Page-Wilson et al. found no change in GLP-1 after RYGB, nor did PYY levels change. Concerning ghrelin, the authors found an increase in fasting ghrelin up to 15 months after RYGB (73). However, Inge et al. showed a steady decrease in peak and basal active ghrelin concentrations up to 14 months after RYGB which could have contributed to the reported decrease in food cravings (72). The positive effects of bariatric surgery on eating behaviour were also reported by Bretault et al. in all three patients. However, its long-term effect was questioned (70).

Thus, further research is necessary to elucidate changes of gut hormone secretion after bariatric surgery for HyOb as an underlying mechanism of weight loss. Nevertheless, as our findings showed inferior results in patients with hypothalamic disturbance compared to non-hypothalamic obesity, it could be questioned whether the central effects of gut hormones after bariatric surgery are preserved if hypothalamic damage is present. Assumption can be made that the observed differences of our findings compared to literature concerning efficacy of bariatric surgery could be attributed to the possibility of heterogeneous damage of hypothalamic structures. As mentioned above, treatment of CP is controversial and depends on its location leading to differences in treatment approach, extent of treatment, additional radiotherapy, complications, possibility of tumour recurrence and necessity of multiple surgeries (8, 11-15, 31). This could influence the degree of tumour- and/or treatment related damage. As the degree of obesity after CP treatment is positively correlated with the extent of hypothalamic damage visualized by MRI (16), a routine MRI might be able to precisely distinct the anatomical degree of hypothalamic damage to evaluate the results of bariatric surgery according to the extent of hypothalamic disturbance.

Secondly, although our findings showed that patients with hypothalamic disturbance profited less of the effects of bariatric surgery, patients treated for CP did lose weight at 2 years of follow-up compared to baseline, suggesting a possible role of non-hypothalamic mechanisms. Schultes et al. reported a case of a craniopharyngioma patient in whom a profoundly damaged hypothalamus visualized on MRI was observed which made preservation of functionally intact hypothalamic structures unlikely. As they expected no effect of gut hormones on the hypothalamus, a distal gastric bypass was performed to create a strong component of malabsorption. However, reduced feelings of hunger, food craving and disinhibition after
surgery were present suggesting that changes in eating behaviour do not only rely on hypothalamic mechanisms (75). Zoicas et al. observed weight loss and improvement in metabolic and cardiovascular risk factors induced by a GLP-1 analogue in all nine patients with hypothalamic obesity in whom six were caused by CP. Although this could indicate heterogeneous hypothalamic damage limited to structures irrelevant for the mechanisms of weight loss by a GLP-1 analogue, it could also be assumed that mechanisms involved do not require intact hypothalamic functioning (122). Indeed, certain mechanisms of bariatric surgery not only exert its effect on the hypothalamus, other regions of the brain which are not affected by the damage of the tumour or its treatment, could play an important role as well. Receptors of ghrelin are found in several other regions besides hypothalamic centres such as the mesolimbic reward circuitry including the ventral tegmental area, responsible for motivational aspects of behaviour like feeding (123). Likewise, a potential role of the orbitofrontal cortex, the striatum, and the insula for example, is highlighted by a reduction in magnetic resonance imaging signals due to a combined administration of PYY and GLP-1 (124). Therefore, although bariatric surgery in patients with hypothalamic disturbance might not be as effective as shown in common obesity, a significant weight loss can still be expected.

2.2. Obesity-related comorbidities

Bariatric surgery has been shown to improve obesity-related comorbidities such as diabetes, hyperlipidaemia, AHT and OSA (67). In patients with CP-related HyOb included in this study, remission of T2DM in one out of two patients after bariatric surgery was observed. A meta-analysis of bariatric surgery for HyOb in patients treated for CP reported a decrease of diabetic patients from 31.6% (6 out of 19 patients) at baseline to 8.3% (1 out of 12 patients) 1 year after surgery (69). Furthermore, a decrease in fasting insulin, HbA1c concentrations and HOMA-IR after gastric bypass surgery has been reported (70, 72, 73, 82), as well as complete remission of diabetes after weight loss induced by sleeve gastrectomy in all three patients included in a more recent study by Trotta et al. (76).

Due to a small sample of patients diagnosed with the abovementioned obesity-related comorbidities, comparison of the improvement of these health consequences between patients treated for CP and control patients included in this matched case-control study would have been clinically and statistically implausible. However, Wijnen et al. did compare the use of antidiabetic, antihypertensive and antihyperlipidemic drugs between patients treated for CP and patients with common obesity and found no differences. A decrease in diabetes medication and antihypertensive drugs was observed, compared to no change of use of lipid-lowering therapy. However, it should be noted that this concerned a decrease in only one out of one diabetic patient treated for CP, a decrease in two out of four patients with AHT and
treated for CP and no decrease in one out of one patient with dyslipidaemia and treated for CP (77). One patient in this study, diagnosed with hypertriglyceridemia, was not able to reduce the lipid-lowering medication after SG either, nor did the baseline lipid evaluation show any signs of remission. However, improvement of hyperlipidaemia and lipid levels in patients treated for CP after gastric bypass surgery has been shown in previous reported cases (72, 74, 82).

Although most of previous studies observed positive metabolic effects of bariatric surgery in patients treated for CP, describing a conclusion of our observations would be implausible due to the limited amount of cases. Also, some variables could have biased the results. For instance, it is not negligible that improvement of lipid profile and insulin sensitivity could be secondary to the magnitude of weight loss (125-129). Therefore, failure of improvement of T2DM and hypertriglyceridemia in our patient could be associated with a lack of weight loss. Furthermore, as it could be criticized that correction of T2DM can occur within days after surgery and reduction in use of diabetes medication can be observed before maximal weight loss has been achieved (130, 131), diabetes remission rates also depend on the severity of the disease. A recent randomized controlled trial reporting 5 year outcomes in patients with T2DM treated with medical intensive therapy only or combined with RYGB or SG, not only showed weight loss by 1 year predictive of remission, a duration of diabetes of less than 8 years was a main predictor of achieving a glycated hemoglobin level of 6.0% (106). Furthermore, a lower HbA1c indicating a better β-cell function, and insulin independency at baseline, is positively associated with improvement or remission (132). Although both diabetic patients included in this study received insulin therapy at baseline, the patient in whom improvement after surgery failed, had a high preoperative glycosylated hemoglobin and a long duration of the condition which could also have attributed to the failure of remission.

Due to lack of patients treated for CP and diagnosed with AHT and the lack of post-surgery polysomnographic results, we were not able to make any statement concerning remission of AHT or OSA. Nevertheless, other cases of bariatric surgery in CP-related HyOb have shown that improvement of these conditions is plausible. Nonetheless, it should be noted that definition of remission or improvement was either not mentioned or based on subjective improvement in case of OSA as resolution of OSA in only one out of four described cases was confirmed by overnight pulse oximetry (71, 74-77).

Thus, although we were not able to draw any conclusions, improvement of obesity-associated health consequences has been observed, but further research including a greater sample size is necessary to elucidate this plausibility.
2.3. Hormone replacement therapy

Only minor adjustments in hormone replacement therapy were observed in all five patients, this could imply that bariatric surgery in patients treated for craniopharyngioma appears to be safe.

In accordance, during a long-term follow-up, minor or no alterations in endocrine supplementation management were necessary to maintain adequate hormone levels in preliminary reports including studies on both SG and gastric bypass surgery (76, 77, 82). Only Weismann et al. reported impaired effectiveness of oral desmopressin in one patient after SG and a possible case of adrenal insufficiency after LAGB (78).

Slight adaptations in hormone replacement therapy due to variations in absorption and altered pharmacokinetics and bioavailability after bariatric surgery according to the route of administration, surgery type and the specific drug type could have been expected. However, there is a lack of medication-specific data regarding the effect of bariatric surgery on drug absorption and bioavailability of oral drugs.

Some studies show a decrease in levothyroxine dose requirements after bariatric surgery, probably correlated to the weight change (133, 134). One aspect of lower dosing of levothyroxine due to weight loss is the possibility that there is a resolution of impaired levothyroxine pharmacokinetics, as impaired pharmacokinetics have been shown in severely obese volunteers due to the higher plasma volume of distribution (135, 136). Secondly, as lean body mass correlates with levothyroxine requirements (137), lower postoperative requirements of levothyroxine are likely to be expected due to decrease of lean body mass after bariatric surgery (133). However, only one patient included in this study had a decrease of levothyroxine dose which was not associated with weight loss. In three out of five patients of whom two underwent RYGB, an increase in dose was documented. It could be hypothesised that malabsorption could have caused this increase in dosing. However, although a significant delay of levothyroxine absorption after RYGB was observed in a recent study, there was no diminished levothyroxine absorption (138). Also, an oral thyroid and hydrocortisone absorption test after gastric bypass surgery in a patient treated for CP performed by Wolf et al. revealed sufficient gastrointestinal drug resorption (82). Above all, assumptions have to be made carefully as non-compliance in our included patients could not be excluded.

Reduction of dose due to weight loss could also be expected for hydrocortisone as clearance depends on bodyweight and body surface area. Prescribing a fixed dose in patients with a decrease in bodyweight could lead to overdosing with weight gain as a side effect (114, 139). However, only a slight decrease in one out of five patients was seen in this study. Although it appears that no studies on the absorption or pharmacokinetics of corticosteroids after bariatric
surgery have been published, altered pharmacokinetics after surgery could compensate the required reduction of hydrocortisone dose due to weight loss. Furthermore, adjustments to steroid dosage not only depend on the bodyweight of the patient, other factors such as signs of hyper- or hypocortisolism are used to manage the hydrocortisone dose as well.

Next to minor changes in endocrine managements, it is imperative to detect other possible postoperative complications after bariatric surgical interventions as they may occur and can bring important sequelae. Vomiting, for example, cannot only cause impaired resorption of medication including hormone replacement therapeutic drugs, it can also be a sign of adrenal insufficiency. In one case included in our study, vomiting after surgery was reported. However, no signs or symptoms of adrenal insufficiency were present. Nevertheless, there has been a case described in literature who presented with vomiting after surgery followed by an adrenal crisis with hospitalization (78).

Thus, until more data on specific drug types are published, closely monitoring patients with surgery-induced weight change in order to detect possible variations of hormone substitution requirements and in order to correct the therapy properly, is necessary.

3. Limitations

3.1. Critical evaluation of the study design

As bariatric surgery has been proven to be effective in common obesity (67), and only one other matched case-control study has been identified (77), a matched case-control design was chosen to compare efficacy of surgery between control patients with common obesity and patients treated for CP. Matching was based on clinical factors which could have affected the weight loss response after surgery and CP and control patients were both operated in the same surgical department according to the same surgical protocol excluding possible differences in surgical approaches between both groups. However, as CP is a rare condition (4), and thus only a minority of patients undergo bariatric surgery after treatment of CP, it is hard to obtain a large sample of participants. Although the sample size in this study was quite large for a single-centre study, interpretation of our results recommends caution. Furthermore, due to the limited sample size, statistical analysis concerning comparison of both surgical procedures between patients treated for CP and controls was not possible. Weight loss after RYGB and SG was based on observation of data only which precludes definite conclusion.
Additionally, the retrospective design further limits this study. Although this is no different to all previous studies concerning this topic, a retrospective design has its known disadvantages. Although the level of completeness of data was quite high, medical reports do not provide detailed information about methods of measurement of the included outcomes. Moreover, it was assumed that the medical reports concerning medication and its dose were accurate and resembled the state of the condition. The possibility of physician and patient nonadherence to treatment recommendations could not be excluded. Also, it was not possible to retrieve information concerning physical activity or nutritional intake of cases nor controls, and there may have been differences between both groups. It could be hypothesised that energy expenditure of patients treated for CP is likely to be lower than controls based on previous studies which showed that energy intake, sympathetic tone based on urine catecholamine metabolites and physical activity was decreased in craniopharyngioma patients (32, 42, 43), indicating the possibility of greater differences in weight loss between both groups than reported in our study.

3.2. External validity

Next to being a single-centre study, the generalisability of this study is further limited by the characteristics of the study participants. CP has a bimodal age distribution with a peak at 5 – 14 years and at 50 – 74 years of age (4). However, study participants did not match this distribution as only one patient was diagnosed in the lower peak. Although bariatric surgery could be delayed until adulthood, as mentioned earlier, early treatment of obesity after hypothalamic surgery could be beneficial to prevent excessive weight gain. A recent review on treatment options for CP-related HyOb including all reports on surgically treated CP-related HyOb, summarized characteristics of craniopharyngioma patients treated with bariatric surgery. They documented 9 out of 40 published cases who had surgery during childhood (140). It should be criticised that assumptions in this matched case-control were about study participants who all had surgery in adulthood. Bariatric procedures in childhood can be controversial and medical, psychological, legal and ethical considerations regarding bariatric procedures in minors should be taken into account (141).
Conclusion and future directions

In conclusion, short term results of bariatric surgery seemed to be superior in patients with non-hypothalamic obesity compared to patients with HyOb after treatment of a craniopharyngioma. Even so, significant weight loss in patients with HyOb after bariatric surgery was plausible. Furthermore, bariatric surgery seemed to be safe in terms of its effect on hormone replacement therapy, although pituitary replacement therapy after bariatric surgery should be closely monitored to prevent side effects.

Given the maximal weight gain shortly after CP treatment, patients diagnosed with craniopharyngioma should be counselled about the risk of developing HyOb and early recognition and management of HyOb should be provided to prevent excessive weight gain. Although less effective in comparison to non-hypothalamic obesity, bariatric surgery cannot be excluded for management of HyOb as conservative treatment seems to be tepid at best (62). To confirm this assumption, further research comparing patients treated with bariatric surgery vs. conservative treatment for CP-related HyOb is necessary. Additionally, as hypothalamic mechanisms could contribute to the weight loss after surgery, the possibility of identifying patients which are most likely to respond best to surgery based on the extent of hypothalamic damage should be further researched.

However, no current generalized accepted therapy for HyOb in CP has been shown to be effective in randomized studies. The limited sample size in this study precludes definite conclusions on the use of bariatric surgery as a treatment modality for hypothalamic obesity in patients treated for craniopharyngioma. Therefore, performing surgery in a tertiary care centre with experienced bariatric surgeons and a multidisciplinary team capable of long-term follow-up including the possibility of participation in studies investigating the outcome of surgery, should be preferred. Well-designed, prospective, multicentre studies with a large sample size and a long-term follow-up could add significant value to the research of management of HyOb including better defining the position of surgery in the treatment of craniopharyngioma-related hypothalamic obesity.

Conflict of interest: The author declares no conflict of interest.
References


121. BCFI : Belgisch Centrum voor Farmacotherapeutische Informatie.


Appendix 1: Tables and charts

Subjects who underwent bariatric surgery from September 2007 to August 2017 at Ghent University Hospital (N>1000)

Inclusion criteria of cases
- obesity after CP treatment
- hypopituitarism

Individually matched by
- gender
- bariatric procedure
- age at BS
- BMI at BS
- date at BS

Exclusion criteria for matched control subjects
- hypothalamic dysfunction (N=1)
- previous bariatric surgery (N=3)
- lack of postoperative data (N=3)
- thyroid disorders, corticoid use… (N=2)
- no consent (N=1)

5 included subjects treated for craniopharyngioma

10 included matched control subjects

Figure 4. Flow diagram of included subjects
Abbreviations: N, number; CP, craniopharyngioma; BS, bariatric surgery
Table 1
Characteristics of patients treated for craniopharyngioma

<table>
<thead>
<tr>
<th>No</th>
<th>G</th>
<th>CP treatment</th>
<th>Age (yr.)</th>
<th>BMI (kg/m²)</th>
<th>Primary treatment</th>
<th>Period CP-recurrence (yr.)</th>
<th>Treatment of tumour recurrence</th>
<th>PHD</th>
<th>Age (yr.)</th>
<th>Period CP-BS (yr.)</th>
<th>Procedure</th>
<th>BMI (kg/m²) at BS</th>
<th>BMI (kg/m²) 2 years after BS</th>
<th>Comorbidity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>26</td>
<td>37,0</td>
<td>TC incomplete resection + IMRT (54 Gy, 27 fractions)</td>
<td>N/A</td>
<td>N/A</td>
<td>Panhyp., DI</td>
<td>27</td>
<td>1</td>
<td>SG</td>
<td>SG</td>
<td>43,2</td>
<td>51,9</td>
<td>N/A</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>28</td>
<td>25,9</td>
<td>TS incomplete resection</td>
<td>1</td>
<td>3DCRT (57,6 Gy, 32 fractions)</td>
<td>Panhyp., DI</td>
<td>40</td>
<td>12</td>
<td>SG</td>
<td>SG</td>
<td>37,9</td>
<td>34,9</td>
<td>T2DM, hyperl., OSA</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>35</td>
<td>35,6</td>
<td>Punction of cyst + TC complete resection</td>
<td>N/A</td>
<td>N/A</td>
<td>Panhyp., DI</td>
<td>36</td>
<td>1</td>
<td>RYGB</td>
<td>RYGB</td>
<td>46,3</td>
<td>36,3</td>
<td>T2DM, OSA</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>12</td>
<td>30,4</td>
<td>Punction of cyst + 3DCRT + intracavitary irradiation (⁹⁰Y)</td>
<td>19</td>
<td>Neuro - endoscopic cyst drainage with residual solid tumour</td>
<td>Panhyp., DI</td>
<td>38</td>
<td>26</td>
<td>RYGB</td>
<td>RYGB</td>
<td>41,3</td>
<td>31,1</td>
<td>IGT, OSA</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>37</td>
<td>19,9</td>
<td>TS complete resection</td>
<td>N/A</td>
<td>N/A</td>
<td>Panhyp., DI</td>
<td>47</td>
<td>10</td>
<td>RYGB</td>
<td>RYGB</td>
<td>40,1</td>
<td>24,3</td>
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</tr>
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</table>

Abbreviations: No., patient number; N/A, not applicable; G, gender; M, male; F, female; CP, craniopharyngioma; BMI, body mass index; TC, transcranial; TS, transsphenoidal; IMRT, intensity modulated radiotherapy; period recurrence 3DCRT, three-dimensional conformal radiation therapy; Gy, gray; period CP-recurrence, time between initial surgery and tumour recurrence; PHD, pituitary hormone deficiency; panhyp. panhypopituitarism; DI, diabetes insipidus; period CP-BS, period between first treatment of craniopharyngioma and bariatric surgery; SG, sleeve gastrectomy; RYGB, Roux-en-Y gastric bypass; T2DM, type 2 diabetes mellitus; IGT, impaired glucose tolerance; hyperl., hyperlipidaemia; OSA, obstructive sleep apnoea

a Morbidity caused by craniopharyngioma or its treatment
b Comorbidity present at bariatric surgery
c Age and BMI at primary treatment
d BMI at treatment of tumor recurrence was used as BMI at primary treatment was missing
Table 3
Hormone replacement therapy before and after bariatric surgery

<table>
<thead>
<tr>
<th>No.</th>
<th>Hydrocortisone (mg/day) (p.o.)</th>
<th>L-thyroine (µg/day) (p.o.)</th>
<th>Sex steroids *</th>
<th>Growth hormone (mg/day) (s.c.)</th>
<th>Desmopressin (mg/day) (p.o.)</th>
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<tbody>
<tr>
<td></td>
<td>BS 6mo. 1yr. 2 yr.</td>
<td>BS 6mo. 1yr. 2 yr.</td>
<td></td>
<td>BS 6mo. 1yr. 2 yr.</td>
<td>BS 6mo. 1yr. 2 yr.</td>
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<td>1</td>
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<tr>
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<td>1 25</td>
<td></td>
<td>Test.</td>
<td>N/A</td>
<td>1.2</td>
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<tr>
<td></td>
<td>20</td>
<td></td>
<td>225</td>
<td>N/A</td>
<td>0.4 0.4 0.4 0.4</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
<td>225</td>
<td></td>
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</tr>
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Abbreviations: No., patient number; N/A, not applicable,

* Sex steroids
  1 = ethinylestradiol 0,02mg / gestodene 0,075 mg (P.O.)
  2 = ethinylestradiol 0,02mg / desogestrel 0,15 mg (P.O.)
  Test. = testosterone (mg/ml/month) (I.M.)

b Route of administration: nasal

Bold values are doses changed compared to the previous observation
### Appendix 2: Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>AHT</td>
<td>Arterial hypertension</td>
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<tr>
<td>ARC</td>
<td>Arcuate nucleus</td>
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<tr>
<td>BMI</td>
<td>Body mass index</td>
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<tr>
<td>BPD</td>
<td>Biliopancreatic diversion</td>
</tr>
<tr>
<td>CP</td>
<td>Craniopharyngioma</td>
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<tr>
<td>CT</td>
<td>Computed tomography</td>
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<tr>
<td>GH</td>
<td>Growth hormone</td>
</tr>
<tr>
<td>GLP-1</td>
<td>Glucagon-like peptide-1</td>
</tr>
<tr>
<td>HbA1c</td>
<td>Glycated haemoglobin</td>
</tr>
<tr>
<td>HDL</td>
<td>High-density lipoprotein</td>
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<tr>
<td>HyOb</td>
<td>Hypothalamic obesity</td>
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<tr>
<td>IGT</td>
<td>Impaired glucose tolerance</td>
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<tr>
<td>LAGB</td>
<td>Laparoscopic adjustable gastric banding</td>
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<tr>
<td>LDL</td>
<td>Low-density lipoprotein</td>
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<tr>
<td>MRI</td>
<td>Magnetic resonance imaging</td>
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<tr>
<td>nCPAP</td>
<td>Nasal continuous positive airway pressure</td>
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<tr>
<td>OGTT</td>
<td>Oral glucose tolerance test</td>
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<tr>
<td>OSA</td>
<td>Obstructive sleep apnoea</td>
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<tr>
<td>PYY</td>
<td>Peptide YY</td>
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<tr>
<td>RYGB</td>
<td>Roux-en-Y gastric bypass</td>
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<tr>
<td>SG</td>
<td>Sleeve gastrectomy</td>
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<tr>
<td>TG</td>
<td>Triglycerides</td>
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<tr>
<td>T2DM</td>
<td>Type 2 diabetes mellitus</td>
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<tr>
<td>%TWL</td>
<td>Percentage of total bodyweight loss since baseline</td>
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</tbody>
</table>
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Appendix 4: Approval Ethics Committee

COMMISSIE VOOR MEDISCHE ETHIEK

Noms/Nummer

Prof. D. Martens

Adres/E-mail

Prof. D. J. DeMeester

Universiteit Gent

Onderwerp

Betreft

Advies voor monoclinische studie met als titel:

Bariatric surgery in patients after resection of antrumpylorregion - surgical lineage history

Advies is gedaan door:

Prof. dr. Y. Van Neerdenheve; Houdbare=ovens

Er wordt een positief advies gegeven over dit protocol op 21/11/2018, waarin de studie niet wordt

wordt gestart voor 21/11/2018, verwacht het advies daarmee het project te zijn begonnen.

Vanaf dan, het onderzoek van een enkel cliënt contactte gemaakt onder de naam (advies #110, 21/11/2018)

De boven genoemde documenten zijn al geverifieerd door de ethics committee.

A positief advies was gegeven voor dit protocol op 21/11/2018. In case this study is not started by 21/11/2018,

Dit advies wordt ondertekend in het verslag van de vergadering van de ethics committee van 21/11/2018.

This advice will appear in the proceedings of this meeting of the ethics committee of 21/11/2018.


Appendix 5: Informed consent

Informatie voor de patiënt:

Project:
Bariatrie bij patiënten na resectie van een craniopharyngeoom

Beschrijving en doel van het project:
U wordt/werd door ons verzorgd in het kader van uw ziekte (craniopharyngeoom – een relatief goedaardige hersentumor).

De dienst Gastro-intestinale Heelkunde voert een onderzoek uit naar de gevolgen van vermageringsoperaties bij zwaarlijvige patiënten na resectie van een craniopharyngeoom.

Na resectie van een craniopharyngeoom kan de functie van verzadigingsgevoel worden verstoord met zwaarlijvigheid tot gevolg. Bij veel patiënten lijkt het moeilijk tot onmogelijk voldoende gewichtsverlies of zelfs gewichtsbeheersing te bekomen. De vraag stelt zich of obesitaschirurgie een zinvolle benadering is. Er is niet alleen de vrees dat de ingreep gepaard gaat met een verhoogde ziekte slag, maar ook dat de vele geneesmiddelen die de patiënten moeten innemen niet voldoende geresorbeerd worden uit het darmstelsel. Verder dient ook nagegaan te worden of de ingreep dezelfde gunstige resultaten geeft bij deze patiënten in vergelijking met mensen met een normale verzadigingsfunctie.

Wij zouden u vriendelijk willen vragen of u de toestemming zou willen geven om prospectief enkele gegevens uit uw dossier te mogen gebruiken voor deze wetenschappelijke analyse. Wij zijn in het bijzonder geïnteresseerd in de evolutie van uw lichaamsgewicht en de dosis van de medicatie die u neemt. Verder willen we ook weten of er andere nadelige gevolgen opgetreden zijn na de vermageringsingreep.

Deze studie werd goedgekeurd door een onafhankelijke Commissie voor Medische Ethiek verbonden aan het UZ Gent, en zal worden uitgevoerd volgens de richtlijnen van ICH/GCP opgesteld in de verklaring van Helsinki opgesteld ter bescherming van individuen deelnemend aan klinische studies. Deze verzameling wordt uitgevoerd door een student in kader van een masterproef onder supervisie van Prof. Dr. Yves Van Nieuwenhove.

Toestemming en weigering
Het staat u volkomen vrij om deel te nemen of niet.

U kunt weigeren zonder dat u hiervoor een reden moet geven en zonder dat dit op enigerlei wijze een invloed zal hebben op uw verdere behandeling en de relatie met de behandelende artsen. Als u toestemt, wordt u gevraagd het toestemmingsformulier te tekenen en naar ons op te sturen (contactgegevens: zie verder, adres: zie begeleidende brief).

Voordelen
Deze studie biedt geen medisch of ander voordeel voor uzelf, maar de bekomen resultaten kunnen leiden tot nieuwe en meer efficiënte methodes voor de behandeling van een craniopharyngeoom en polyfagie/obesitas ten gevolge van de resectie van het craniopharyngeoom.

Kosten
Uw deelname aan de studie brengt geen bijkomende kosten mee voor u, maar biedt ook geen financieel voordeel.

Vertrouwelijkheid
Als u akkoord gaat om aan deze studie deel te nemen, zullen uw persoonlijke en klinische gegevens tijdens deze studie worden geanonimiseerd (hierbij is er totaal geen terugkoppeling meer mogelijk naar uw persoonlijke dossier). In overeenstemming met de Belgische wet van 8 december 1992 en de
Belgische wet van 22 augustus 2002, zal uw persoonlijke levenssfeer worden gerespecteerd. Als de resultaten van de studie worden gepubliceerd, zal uw anonimiteit aldus verzekerd zijn.

**Verzekering**
De experimentenwet van 07/05/2004 verplicht ons om deelnemers aan wetenschappelijke projecten te verzekeren voor de deelname en het risico (hoe klein ook) dat men loopt. De waarschijnlijkheid dat u door deelname aan deze studie enige schade ondervindt, is extreem laag. Indien dit toch zou voorkomen, wat echter zeer zeldzaam is, werd er een verzekering afgesloten conform de Belgische wet van 7 mei 2004, die deze mogelijkheid dekt.

**Contactgegevens**

Professor Yves Van Nieuwenhove 09/332.48.93  
Student Ieme Garrez 0496/13.86.04  
Studiedienst: Inge Vandenbroucke 09/332.94.92  
Patricia Horckmans 09/332.42.52
TOESTEMMININGSVERKLARING

Mevrouw/De Heer..............................................................................................................

Ik stem erin toe vrijwillig deel te nemen aan dit wetenschappelijk onderzoek.

Ik verklaar hierbij op een begrijpelijke wijze mondeling en schriftelijk te zijn ingelicht over de aard, de methode en het doel van deze studies.

Ik ben me ervan bewust dit project beoordeling en controle aan het Ethisch Comité van het UZ Gent werd voorgelegd.

Ik ben ervan op de hoogte dat deelname aan deze studie geen bijkomende kosten meebrengt en dat er geen financieel voordeel aan verbonden is.

Ik kan me op elk moment terugtrekken tot op het ogenblik dat de gegevens in de database worden bewaard, zonder hiervoor een verklaring te hoeven afleggen en zonder dat dit op enigerlei wijze invloed zal hebben op de verdere behandeling en de relatie met de arts.

Gelezen en goedgekeurd,

Datum:........................

Dr. .............................  Naam patiënt........................

(Naam en handtekening)