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Pharmacokinetics of Glucocorticoid Replacement Before and After Bariatric Surgery in Patients With Adrenal Insufficiency

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Adequate glucocorticoid replacement in patients with primary or secondary adrenal insufficiency is essential to maintain general well-being. Little is known about the effects of bariatric surgery on glucocorticoid absorption. This study evaluates glucocorticoid absorption before and after bariatric surgery, with assessment of plasma cortisol profiles in five patients receiving glucocorticoid replacement therapy for primary (n = 1) or secondary (n = 4) adrenal insufficiency. One patient underwent sleeve gastrectomy (SG), one a one-anastomosis gastric bypass (mini-GB), and three a Roux-en-Y gastric bypass (RYGB). Pharmacokinetic calculations were based on plasma cortisol measurements performed during the first 6 hours after ingestion of the morning dose. Plasma cortisol profiles were very similar before and after surgery; only minor differences were observed. After SG, plasma peak cortisol concentration and cortisol area under the curve (AUC) were higher by 23% and 24%, respectively, and time to peak cortisol was 10 minutes shorter. The mini-GB had no marked effect on pharmacokinetic parameters. In the three patients who underwent RYGB, AUC changes ranged from −12% to 20%. In conclusion, in this small number of patients with adrenal insufficiency, plasma cortisol profiles were similar before and after bariatric surgery. However, in view of individual differences in response to different types of surgery, we recommend postoperative cortisol profiling to guide appropriate glucocorticoid dose adjustment.

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Bariatric surgery is the most effective treatment to achieve clinically substantial long-term weight loss in people who are morbidly obese [1]. When the procedure is performed with laparoscopic techniques, perioperative morbidity and mortality are very low [2]. Recently, these procedures have been shown to be successful in patients with hypothalamic obesity who received hormonal replacement therapy for pituitary failure [3–5]. However, on theoretical grounds bariatric surgery is not without risk in these patients. The surgically altered

Abbreviations: AUC, area under the curve; mini-GB, one-anastomosis gastric bypass; RYGB, Roux-en-Y gastric bypass; SG, sleeve gastrectomy.

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anatomy will reduce gastrointestinal transit time as well as digestion and absorption surface, and this may compromise medication bioavailability [6]. In patients with primary or secondary adrenal failure, adequate absorption of oral glucocorticoids is essential for well-being and survival. Unfortunately, current knowledge of glucocorticoid absorption after bariatric surgery is very limited, creating uncertainty among clinicians who are asked to give advice on the risks of bariatric surgery in glucocorticoid-dependent patients.

In theory, it is conceivable that bariatric surgery not only may reduce absorption quantitatively and increase the risk for Addison crises but also adversely affects the pattern of absorption. Faster absorption due to rapid gastric emptying could lead to higher plasma peak cortisol levels and cause intermittent overexposure to glucocorticoids, with possibly detrimental side effects in the long run. It is therefore important to increase the knowledge of the pharmacokinetics of glucocorticoid replacement therapy after bariatric surgery.

The current study describes the plasma cortisol response after orally administered glucocorticoids in four patients with secondary adrenal insufficiency and in one patient with Addison disease before and after various types of bariatric surgery.

1. Patients and Methods

Glucocorticoid absorption was evaluated in five patients who were morbidly obese: four with secondary adrenal insufficiency and one with Addison disease. They had been referred to our centers for bariatric surgery. They all met the criteria for bariatric surgery as defined by the International Federation for the Surgery of Obesity and Metabolic Disorders [7]. After explanation of the importance of monitoring glucocorticoid requirements after surgery, all patients gave their informed consent to undergo hydrocortisone absorption tests before and after surgery. The study was approved by the local ethical committee of the Rijnstate Hospital (study number 2018-1220).

Absorption tests started at 8:00 AM after an overnight fast. Preoperative testing was performed 1 to 3 weeks before surgery, and postoperative tests were done in the first or second week after surgery. Blood samples were obtained by an IV cannula inserted in an antecubital vein. After baseline sampling, patients ingested hydrocortisone (four patients) or cortisone-acetate (one patient). Four patients (patients 1 to 4) were tested while taking their usual glucocorticoid replacement doses. A daytime cortisol profile was obtained in patients 1 and 2, with frequent blood sampling at 10, 20, 30, 40, 50, 60, 120, 180, 240, 300, and 360 minutes after ingestion of the morning and midday dose [Fig. 1(A) and 1(B)]. A 24-hour profile with less intensive sampling was performed in patients 3 and 4 [Fig. 1(C) and 1(D)]. In addition, three patients (patients 3 to 5) were tested with a standard dose of 25 mg hydrocortisone to obtain a 12-hour hydrocortisone absorption profile before and after surgery, with samples taken at 30 and 60 minutes and then every 1 to 2 hours (Fig. 2). All samples were temporarily stored to be analyzed later in one run.

Plasma cortisol was measured immediately after the last blood withdrawal by using a competition assay with a Roche Modular E170 module (Roche Diagnostics GmbH, Mannheim, Germany).

Area under the curve (AUC) in the first 6 hours after ingestion of the morning dose was calculated by using SPSS software, version 24.0 (IBM Inc., Armonk, NY). Maximal concentration and time to maximal concentration were derived from the data. Because this was an explorative study, no statistical evaluation was performed.

2. Results

Patient characteristics are summarized in Table 1. All patients with secondary adrenal insufficiency had been treated with pituitary surgery for acromegaly, craniopharyngioma, meningioma, or germinoma. Three of four had multiple pituitary deficiencies.

The preoperative body mass index at the time of study ranged from 37.3 to 47.0 kg/m^2. One patient underwent a sleeve gastrectomy (SG), one a one-anastomosis gastric bypass

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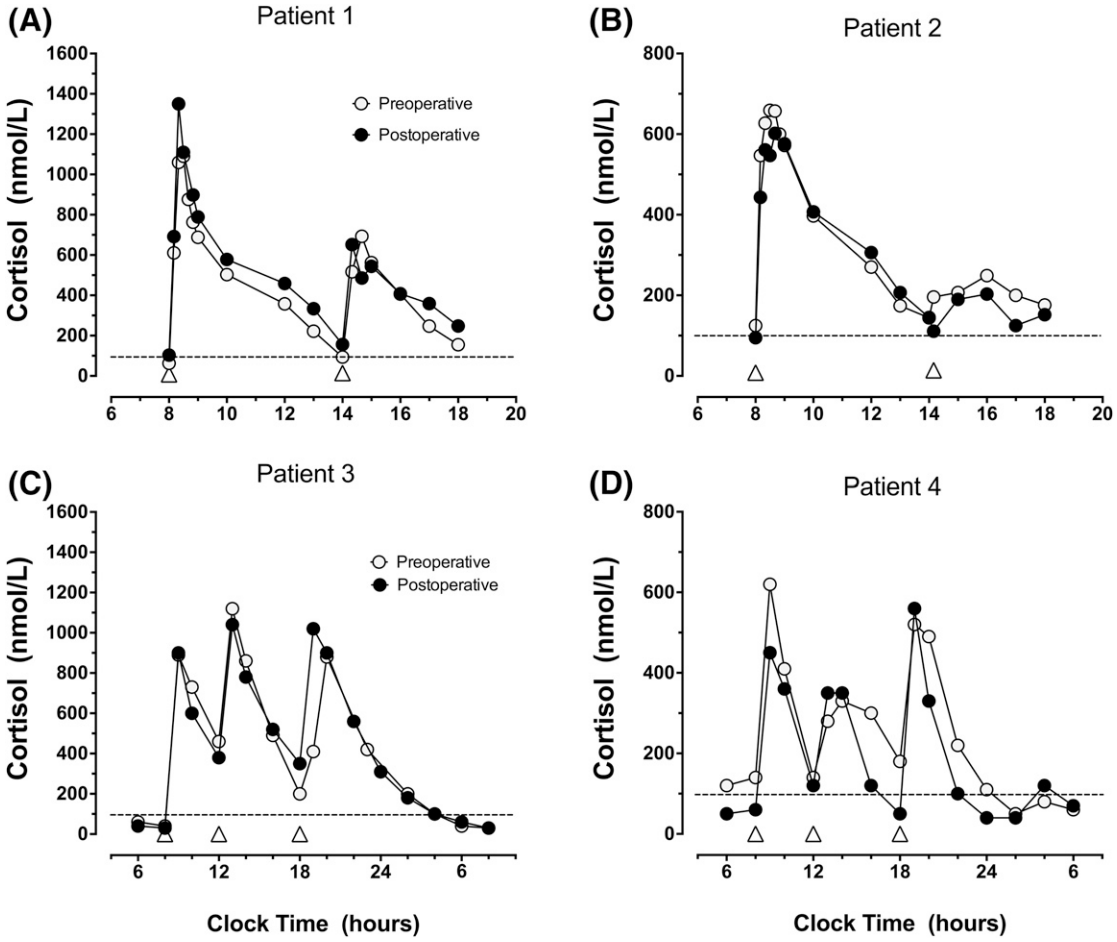

Figure 1. Daytime and 24-h cortisol levels before and after bariatric surgery.

(mini-GB)m and three a Roux-en-Y gastric bypass (RYGB). None of the patients experienced any perioperative complications.

The pre- and postoperative cortisol profiles of patients using their normal daily dose are shown in Fig. 1. Figure 1(A) shows the results of a patient with SG using hydrocortisone at a dose of 30 + 20 mg. The patient in Fig. 1(B) had a mini-GB and used cortisone-acetate at 25 + 12.5 mg. The patients in Fig. 1(C) and 1(D) had an RYGB and used hydrocortisone at 10 mg three times a day.

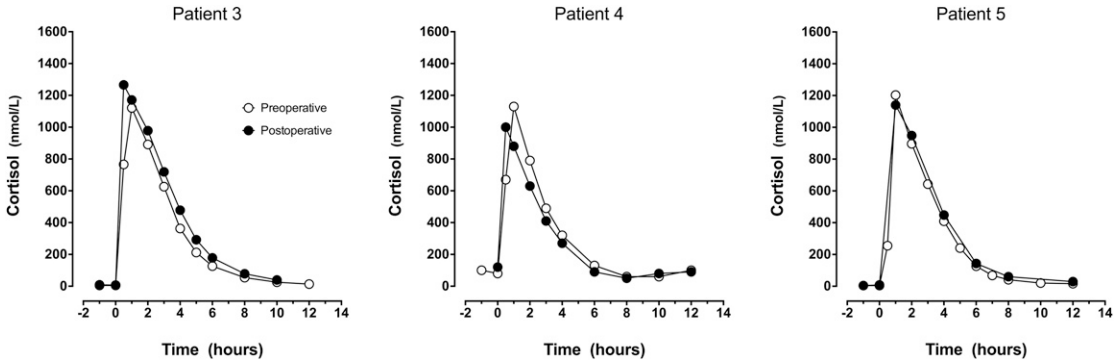

Figure 2. Cortisol levels after a 25-mg oral dose of hydrocortisone, before and after RYGB.

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Table 1. Patient Characteristics

Patient No.	Sex	Age (y)	Diagnosis	Pituitary Insufficiency	Medication	Bariatric Procedure	BMI (kg/m^2)
1	Male	56	Craniopharyngioma OSAS	Panhypopituitarism	HC, 30-20 mg Thyroxine Testosterone Desmopressin	GS	37.3
2	Female	50	Acromegaly	Adrenal	CA 25, 12.5 mg	Mini-GB	40.1
3	Female	39	Meningioma third ventricle	Panhypopituitarism	HC 10-10-10 Thyroxine	RYGB	46.0
4	Female	20	Germinoma third ventricle	Panhypopituitarism	HC 10-7.5-5 Thyroxine Estrogen/PG GH desmopressin	RYGB	47.0
5	Female	48	Addison disease	None	HC 15-7.5-5 Fludrocortisone	RYGB	40.8

BMI, body mass index; CA, cortisone acetate; estrogen/PG, combination of estradiol and progesterone; HC, hydrocortisone, OSAS, obstructive sleep apnea syndrome.

The results of 12-hour cortisol profiles after a single 25-mg hydrocortisone dose in three patients (patients 3 to 5) before and after RYGB are shown in Fig. 2. All obtained cortisol profiles were similar before and after surgery in all patients, with only minor differences.

AUC data of cortisol levels measured for 6 hours after the morning dose, along with other characteristics, such as time to maximum and maximum cortisol concentration, are presented in Table 2.

In the patient who underwent GS, peak cortisol level increased by 23%, AUC increased by 24%, and time to maximum cortisol concentration was 10 minutes shorter after surgery. The patient with the mini-GB had minimal changes in AUC and peak cortisol concentration after surgery but an increase in time to peak cortisol from 30 to 40 minutes. In the three RYGB patients receiving a single 25-mg hydrocortisone dose, AUC results varied from −12% to 20%. Maximum observed concentration and time to maximum observed concentration could not be reliably estimated because of the limited number of measurements during the first hour of the test.

3. Discussion

In this small study of five patients with primary or secondary adrenal failure, cortisol profiles obtained before and after different types of bariatric surgery were roughly similar. The small differences that were observed are unlikely to be of clinical significance. A larger, and preferably controlled, study with patients who are morbidly obese tested with equal hydrocortisone doses will be needed to quantify possible differences in absorption more accurately and to assess whether changes in absorption are related to the type of surgical procedure or result from random variation.

Adequate glucocorticoid replacement therapy is difficult to achieve, even in patients with a normal gastrointestinal tract and without morbid obesity. Interindividual requirements vary markedly, and there are no generally accepted parameters to guide dose adjustments. It is well established that underreplacement may lead to poor quality of life and that

Table 2. Pharmacokinetic Parameters of Cortisol After Oral Ingestion Before and After Bariatric Surgery

Variable	GS Before	GS After	Δ (%)	Mini-GB Before	Mini-GB After	Δ (%)	RYGB Before	RYGB After	Δ (%)	RYGB Before	RYGB After	Δ (%)	RYGB Before	RYGB After	Δ (%)
AUC, nmol/h/L	2428	3027	24	1980	1934	−2	3092	2725	−12	3455	3596	4	3380	4069	20
T-max, min	30	20	−10	30	40	10	60[a]	40[a]		60[a]	60[a]		60[a]	30[a]	
C-max	1090	1350	23	659	602	−0.8	1130[a]	1000[a]	−11	1203[a]	1140[a]	−5	1121[a]	1266[a]	13

Δ, difference before and after in percentages; C-max, maximum observed concentration; T-max; time to maximum observed concentration.

[a]For T-max and C-max in RYGB patients: only values at 0, 30, and 60 min were available.

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overreplacement is associated with increased morbidity and mortality [8]. Various authors advocate the use of plasma cortisol profiles during the day to optimize hydrocortisone replacement therapy in nonsurgical patients [9, 10]. We used cortisol profiling to assess whether glucocorticoid dose adjustments might be necessary after bariatric surgery. Gastric sleeve, mini-GB, and RYGB have in common a partial gastrectomy, which leaves a small pouch that accelerates delivery of medication to the small intestine. In theory, this might change the plasma concentration profiles and create an earlier and higher peak followed by inappropriate low levels in the hours thereafter. Higher peak cortisol levels, as well as suboptimal levels thereafter, may both have clinical consequences. A 23% increase in cortisol peak level was observed in the patient after SG, and this may lead to overexposure in the long run. In contrast to our theoretical considerations, postpeak levels were not decreased.

Studies on cortisol absorption in human prison volunteers, performed by infusion of solutions with different concentrations directly in the lumen of the small intestine, show that the rate of absorption is proportional to the concentration over a 2000-fold range [11]. It was also shown that cortisol absorption is maximal in the proximal part of the small intestine (<200 cm from the oral cavity) and is more than halved in more distal parts. After RYGB and mini-GB surgery, the proximal part of the small intestine is bypassed and food and medication will enter more distally. This might affect glucocorticoid absorption. However, the three RYGB patients who were tested with a 25-mg dose of hydrocortisone showed only minor changes in absorption, without a consistent pattern. Two had a small increase in cortisol availability, whereas one patient demonstrated a small decrease in cortisol AUC. It is not known whether these individual differences are due to the surgery or can be explained by biological (day-to-day) variation of cortisol uptake, cortisol binding to cortisol-binding globulin, cortisol to cortisone conversion, or cortisol clearance.

Studies on glucocorticoid requirements in patients that are morbidly obese before or after surgery are very scarce. We found only three case studies, all lacking dose adjustments based on cortisol measurements [4, 12, 13].

Schultes *et al.* [4] described a single patient with craniopharyngioma with a 54-kg weight loss in 1 year after an RYGB, allowing a gradual decrease in hydrocortisone dose from 30 to 15 mg/d without symptoms of adrenal insufficiency.

Wolf *et al.* [12] reported a retrospective study of four patients with craniopharyngioma with panhypopituitarism, evaluated after RYGB with a mean weight loss of 35 kg (range, 20 to 72 kg). Postoperative hydrocortisone dose adjustments were based on clinical judgement only. The daily hydrocortisone dose was decreased from 50 to 25 mg in one patient, increased in two patients (from 17.5 to 25 mg and from 20 to 25 mg, respectively), and remained unchanged in the fourth patient with a dose of 30 mg/d. None developed adrenal insufficiency. Postoperative hydrocortisone absorption testing was performed in one patient. A single 20-mg oral dose of hydrocortisone caused a high peak plasma cortisol at 30 minutes of 1225 nmol/L, suggesting overreplacement. Conclusions on changes in requirements were impossible because preoperative cortisol data were not available.

In another observational study in eight patients with craniopharyngioma, five used hydrocortisone substitution [13]. According to the authors, no dose adjustments were required, and none of the patients experienced an Addison crisis during a 2-year follow-up. Data on cortisol levels were not available. Weight loss in patients with craniopharyngioma after RYGB (n = 5) was similar to that in obese surgery controls, whereas weight loss after SG (n = 3) was significantly less. Increased exposure to cortisol due to nonadjustment of hydrocortisone doses may have played a role in the suboptimal weight loss in these SG patients.

On the basis of our current experience, we recommend that dose adjustments in patients that are morbidly obese should be individualized according to daily profiles, before as well as after surgery. It has been shown that cortisol clearance is inversely related to insulin sensitivity and that fatty liver disease is associated with increased cortisol clearance, possibly through changes in activity of the 5α-, 5β-reductase and 11β-hydroxysteroid dehydrogenase type 1 in the liver [14–16]. Because most patients who are morbidly obese have fatty liver disease as well as decreased insulin sensitivity, there are at least two factors increasing

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cortisol clearance. Changes in cortisol distribution volume may also have clinically relevant effects. The potential importance of altered pharmacokinetics is illustrated in a case study of a patient with congenital adrenal hyperplasia [17]. A 60-kg weight loss after SG was associated with a 27% decrease in cortisol distribution volume, a 43% decrease in clearance, and a 75% increase in cortisol AUC. The reverse will probably occur when patients become more obese. Therefore, cortisol requirements are likely to be higher in patients who are morbidly obese because of a higher distribution volume and accelerated clearance. In our experience, however, patients that are morbidly obese with adrenal insufficiency who have been referred to our centers for bariatric surgery were often receiving hydrocortisone doses as advised for persons that are nonobese, or even less. Their fatigue and lack of stamina are usually attributed to the impact of excess weight, without considering the possibility of underreplacement. In the past years we have encountered several patients showing marked improvement in physical and mental performance after preoperative hydrocortisone dose adjustments guided by plasma and salivary cortisol levels (data not shown). We therefore recommend that cortisol profiling should be performed both before and after surgery. With an average of 30% total weight loss in the first year after bariatric surgery, cortisol distribution volume and clearance can be expected to decrease substantially, and this may lead to excessive cortisol exposure with its well-known detrimental effects.

In conclusion, the limited data that are available suggest that absorption of glucocorticoids after bariatric surgery is roughly similar to that before surgery, although differences may exist between GS and RYGB. A review of the literature indicates that postoperative weight loss may reduce cortisol requirements considerably because of changes in distribution volume and cortisol clearance. To avoid under-replacement in the preoperative period and over-replacement in the postoperative period, we recommend glucocorticoid dose adjustment based on multiple daytime cortisol measurements.

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