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ORIGINAL CONTRIBUTIONS

Differences in Anthropometric and Metabolic Parameters Between Subjects with Hypoglycaemia and Subjects with Euglycaemia After an Oral Glucose Tolerance Test Six Months After Laparoscopic Sleeve Gastrectomy

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Abstract
Background Hypoglycaemia after an oral glucose tolerance test (OGTT) can occur in up to 33 % of subjects after laparoscopic sleeve gastrectomy (LSG). The underlying pathophysiology is not well understood. We aimed to compare the anthropometric and metabolic characteristics of subjects with post-OGTT hypoglycaemia (HYPO) to subjects with post-OGTT euglycaemia (EU) 6 months after LSG.
Methods Eighteen morbidly obese patients with normal glucose tolerance (NGT) were evaluated with an OGTT before and 6 months after LSG. Serum glucose and insulin were measured before and every 30 min after glucose ingestion up to 120'. The patients were categorized as HYPO or EU based on lowest glucose levels 90' to 120' post-OGTT 6 months after LSG (hypoglycaemia defined as glucose levels <60 mg/dl). OGTT derived indices of insulin secretion; insulin sensitivity and beta cell function were also evaluated.
Results Eight patients (44.4 %) were categorized as HYPO. Preoperatively, subjects with HYPO had lower BMI ($p=0.02$) compared to that with EU. Postoperatively, subjects with HYPO had lower BMI ($p=0.01$), lower weight ($p=0.01$), and higher percentage of total weight loss (%TWL) ($p=0.03$) compared to that with EU. The beta cell function index was higher in the HYPO group postoperatively compared to EU ($p=0.02$)—especially during the latter portion of the OGTT. No difference was detected in insulin secretion and insulin sensitivity indices between the two groups preoperatively or postoperatively.
Conclusions Subjects with NGT who developed HYPO 6 months after LSG are leaner, with higher TWL% and higher beta cell function at the latter portion of the OGTT compared to those with EU.

Keywords Hypoglycaemia · Sleeve gastrectomy · Bariatric surgery · Oral glucose tolerance test

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Introduction

Laparoscopic sleeve gastrectomy (LSG) is a relatively new bariatric procedure which can result in a total weight loss of 20–30 % [1]. The majority of patients will maintain a satisfactory weight loss more than 5 years after the procedure [2] with significant improvement in metabolic comorbidities such as type 2 diabetes mellitus (T2DM), hypertension, and dyslipidaemia [1, 3]. While the favorable outcomes and safety profile of LSG have led to an increasing use of the procedure worldwide during the last decade (27 % of the total bariatric procedures worldwide in 2013) [4], the metabolic and nutritional consequences of the operation are also becoming increasingly recognized.

Postprandial hypoglycaemia, one of the most deliberating complications of Roux-en-Y gastric bypass (RYGB) has been reported to occur also after LSG [5, 6]. The incidence of hypoglycaemia after an oral glucose tolerance test (OGTT) can be as high as 33 % [5] and appears more common in patients with normal glucose tolerance (NGT) preoperatively [6]. More importantly, despite that postprandial hypoglycaemia after LSG may be less common compared to RYGB [7], still

17.8 % of patients experience symptoms highly suggestive of hypoglycaemia in their daily life after LSG [8].

Therapeutic approaches to prevent hypoglycaemia following bariatric surgery are not standardized and comprise dietary interventions, drugs, such as acarbose, diazoxide, or verapamil, as well as invasive procedures in some extreme cases such as subtotal or total pancreatectomy [8–10]. The current literature on the pathophysiology of postprandial hypoglycaemia after LSG is very limited and poorly understood [5, 6, 8]. The purpose of this study was to compare preoperative and postoperative anthropometric and metabolic parameters between a group of subjects with post-OGTT hypoglycaemia (HYPO) to those with post-OGTT euglycaemia (EU) 6 months after LSG. Learning more about the phenotype and the pathophysiological mechanisms underlying the postprandial hypoglycaemia after LSG may help us to identify earlier patients with high risk for hypoglycaemia and, therefore, to develop new treatments for this metabolic complication.

Methods

The present study is a retrospective analysis of prospectively collected data of 18 morbidly obese patients (3 male, 15 female) with normal glucose tolerance test preoperatively (defined as fasting glucose <110 mg/dl, glucose 120′ <140 mg/dl) who underwent LSG at the University Hospital of Larissa, Greece. The study was conducted in compliance with the Declaration of Helsinki. Written consent was obtained from each patient and the institutional review board approved the study.

The inclusion criteria for this study were based on the 1991 National Institute of Health consensus criteria for bariatric surgery [11]. The LSG was performed as previously described [12], with dissection starting approximately 5 cm from the pylorus and extending up to the left crus using a 36F bougie to create the gastric sleeve. No one of the patients was on oral glucose lowering medications for diabetes (metformin, sulphonylureas, acarbose, glitazones, or dipeptidyl peptidase-4 inhibitors), GLP-1 receptor agonists, insulin, oral steroids, or b-blocker.

Relevant for the study data were assessed preoperatively and at 6 months after LSG. Patients arrived at the hospital in the morning, after an overnight fast and an intravenous cannula was placed. A 2-h OGTT with 75 g of glucose (150 ml of noncarbonated glucose drink) was performed. Blood samples were collected at 0 (before oral glucose intake) and at 30, 60, 90, and 120 min after oral glucose intake for the measurement of glucose and insulin levels. Post-load glucose and insulin levels were expressed by calculation of the total area under the curve (AUC) using the trapezoidal rule. Post-load hypoglycaemia was defined as glucose levels <60 mg/dl at 90’ or 120’ after OGTT, independently of whether the patient had symptoms suggestive of hypoglycaemia or not. This biochemical definition of hypoglycaemia is divergent to the defined Whipple triad for hypoglycaemia [13]; however, blood glucose levels below 60 mg/dl has been shown on a number of physiological studies that can result in counter regulatory responses [14]. Moreover, multiple previous studies have used the cutoff of 60 mg/dl in glucose levels—independently of symptoms—to define the postprandial hypoglycaemia after bariatric surgery during an OGTT or mixed meal test [15–17]. The occurrence of dumping syndrome symptoms was monitored during the OGTT preoperatively and postoperatively with the use of two questionnaires—the Sigstad score and Arts’ questionnaire—as have been previously described [18].

Indices to assess insulin sensitivity, insulin secretion, and beta cell function were also evaluated from the OGTT. The homeostatic model assessment of insulin resistance (HOMA-IR) and the insulin sensitivity index (Matsuda index) $(10{,}000 / \sqrt{([(G0 \times I0) \times (Gmean \times Imean)])}$ were calculated to estimate insulin resistance and insulin sensitivity, respectively [19, 20].

Early phase insulin release was estimated by the ratio [insulin AUC (0–30)/glucose AUC (0–30)]. Late phase insulin secretion was estimated by the ratio [insulin AUC (60–120)/glucose AUC (60–120)] and total insulin secretion (0–120) was measured by the ratio [insulin AUC (0–120)/glucose AUC (0–120)] [21].

Because insulin secretion is determined in part by the prevailing insulin sensitivity, the oral disposition index (ODI), which is the product of insulin sensitivity and insulin secretion, yields a reliable measure of β-cell function [21–23]. ODI (0–30) was calculated by the Matsuda index for insulin sensitivity and the index for early phase insulin secretion [(insulin AUC (0–30)/glucose AUC (0–30)]. ODI (60–120) was calculated by the Matsuda index and the late phase insulin secretion index, and ODI (0–120) was calculated by the Matsuda index and total insulin secretion (0–120) index.

Fasting serum concentrations of blood lipids (triglycerides, total cholesterol, high-density lipoprotein (HDL) cholesterol, and low-density lipoprotein (LDL) cholesterol) were determined by routine laboratory methods in the University Hospital of Larissa at baseline and 6 months postoperatively. Haemoglobin A1C (HbA1C) was measured only at baseline.

Insulin and glucose samples were collected in silicone coated plastic serum tubes (BD Vacutainer) containing clot activator. Samples were centrifuged, and serum insulin and glucose levels were measured immediately after the collection. Serum insulin was measured in University Hospitals of Larissa using the Roche Modular system and the electrochemiluminescence immunoassay kit (Roche Diagnostics, UK). This assay showed .05 % cross-reactivity to intact human proinsulin and the primary circulating split form created by processing of the insulin prohormone [24].

Serum glucose concentrations were measured using an Olympus AU 2700 analyzer (Olympus UK, London, UK) incorporating an automated hexokinase method with ultraviolet detection at 340 nm.

Statistical Analysis

The AUC was calculated using the trapezoidal rule, with a y-axis baseline at zero. Continuous variables are presented as mean ± SD if normally distributed, otherwise as median [interquartile range (IQR)]. For continuous variables, the comparisons between subjects with HYPO and EU were calculated by unpaired student's *t* test for normally distributed variables otherwise by Mann Whitney *U* test. Categorical variables were compared by Fischer's exact test. Correlations were explored by Spearman's rank method.

All the statistical analysis was performed in GraphPad Prism 5.0 (GraphPad Software, San Diego, CA).

Results

We divided the patients into two groups according to their glycaemic condition at 90′ to 120′ during the postoperative OGTT (HYPO/EU), and we compared the preoperative and postoperative anthropometric and metabolic parameters between the two groups as well as the change from baseline (delta) in these parameters between the two groups. Postload hypoglycaemia was detected in 8 out of 18 NGT individuals (44.4 %) 6 months after LSG.

Preoperatively, patients with HYPO had significantly lower BMI ($p = 0.02$) and a trend for lower weight ($p = 0.06$) compared to patients with EU (Table 1). There was no difference between the two groups in waist circumference, HbA1C, and dumping symptoms preoperatively.

Six months after LSG, subjects in the HYPO group had lower weight and BMI (both $p = 0.01$) and higher percentage of total weight loss (%TWL) ($p = 0.03$) and percentage of excess BMI loss (%EBMIL) ($p = 0.006$) compared to subjects with EU (Table 1). The delta weight and the delta BMI were almost identical in the two groups 6 months after the operation (Table 1). Interestingly, all patients with BMI ≤29 kg/m^2 at 6 months postoperatively developed hypoglycaemia after an OGTT ($n = 6$), making a BMI cutoff of 29 kg/m^2 100 % specific for hypoglycaemia and 75 % sensitive [Fischer's exact test, ($p = 0.002$)]. There was also a trend for lower waist circumference ($p = 0.08$, Table 1), lower triglycerides ($p = 0.07$, Table 1), and higher Sigstad score ($p = 0.09$, Table 1) in the HYPO group compared to the EU group at 6 months after LSG. However, symptoms suggestive of late dumping (hypoglycaemia) were not significantly different between the two groups postoperatively ($p = 0.39$, Table 1). The majority of subjects with HYPO had very mild symptoms related to hypoglycaemia or was asymptomatic.

Fasting and postprandial glucose levels were almost identical preoperatively between the two groups (Table 2, Fig. 1). Moreover, fasting and postprandial insulin levels as well as the insulin secretion, insulin sensitivity, and insulin resistance indices were not significantly different between the two groups (Table 2, Fig. 1).

Postoperatively, glucose levels were significantly lower at time points 90′ and 120′ during the OGTT ($p = 0.02$, $p < 0.001$, respectively, Fig. 2) for the individuals in the HYPO group. The calculated glucose AUC (0–120) and the glucose AUC (60–120) were lower in subjects with HYPO compared to subjects with EU ($p = 0.04$ and $p = 0.004$, respectively, Table 2). Similarly, the change from baseline (delta) for glucose AUC (0–120) and glucose AUC (60–120) was lower for the HYPO group compared to the EU (Table 2).

Postoperatively, fasting and post-load insulin levels, as well as insulin AUC (0–120), were not different between the two groups (Table 2). Moreover, the change from baseline for fasting and post-load insulin levels was also not significantly different between the two groups (Table 2).

As far as insulin secretion, insulin sensitivity, and insulin resistance after LSG, no difference was detected postoperatively between the two groups (Table 2). This was also the case when comparing the same parameters for change from the baseline (delta) between the two groups (Table 2). Oral disposition indices [ODI (0–120) and ODI (60–120)] postoperatively as well as delta ODI (0–120) and delta ODI (60–120) were significantly elevated in the HYPO group compared to the EU group (Table 2).

A negative correlation was found between postoperative ODI (60–120) and postoperative weight ($r = -0.51$, $p = 0.03$), BMI ($r = -0.51$, $p = 0.03$), and HOMA-IR ($r = -0.77$, $p < 0.01$), and there was a trend for negative correlation with postoperative glucose AUC (60–120) ($r = -0.44$, $p = 0.06$). On the other hand, a negative correlation was found between postoperative ODI (0–120) and postoperative HOMA-IR ($r = -0.49$, $p = 0.03$) and glucose AUC (60–120) ($r = -0.73$, $p < 0.001$). A trend for positive correlation between postoperative Matsuda index and postoperative ODI (0–120) ($r = 0.44$, $p = 0.06$) was observed.

There was also a positive correlation between the postoperative BMI and the postoperative nadir glucose levels ($r = 0.67$, $p = 0.002$), when there was no correlation between the change in BMI from baseline (delta BMI) and the nadir glucose levels postoperatively ($r = 0.19$, $p = 0.43$).

Discussion

The aim of this study was to identify any differences in clinical and metabolic characteristics between normoglycaemic

Table 1 Demographic, anthropometrics, dumping scores and lipid levels for patients who underwent post-OGTT hypoglycaemia and post-OGTT euglycaemia during the postoperative OGTT

		Hypoglycaemic ($n = 8$)	Euglycaemic ($n = 10$)	p value
Gender	(M/F)	2/6	1/9	0.4
Age	(Years)	36.5 ± 11.06	41.9 ± 9.58	0.28
Height	(cm)	168.6 ± 8.73	168.4 ± 7.98	0.95
Weight	(Kg)			
Baseline		119.6 ± 18.84	137.8 ± 18.44	0.06
6 months		76 (72.5–87.8)	101.3 (89.8–115.8)	0.01
Change from baseline		−36 [−39.25–(−34)]	−37 [−39.25–(−29.75)]	0.93
BMI	(Kg/m^2)			
Baseline		41.82 ± 3.19	48.66 ± 6.54	0.02
6 months		28.38 ± 4.05	36.07 ± 6.67	0.01
Change from baseline		−12.99 [−14.29–(−11.58)]	−12.99 [−13.49–(−11.77)]	0.90
EBMIL	(%)	81.96 ± 18.82	56.59 ± 15.11	<0.01
TWL	(%)	32.24 ± 6.54	26.19 ± 4.71	0.03
Waist circumference	(cm)			
Baseline		123.3 ± 15.56	129 ± 13.67	0.37
6 months		89 (85.5–99)	102.5 (97–117.8)	0.08
Change from baseline		−30.25 ± 9.22	−25.78 ± 10.12	0.36
Total cholesterol	(mg/dl)			
Baseline		211 (202–221)	184.5 (157.8–220.8)	0.13
6 months		209 (178.3–245.3)	178 (156–212)	0.24
Change from baseline		−8 (−42–2)	6 (−31–44)	0.41
Triglycerides	(mg/dl)			
Baseline		128 (122–162)	117 (74.25–208)	0.74
6 months		80 ± 22.48	115.1 ± 45.1	0.07
Change from baseline		−48 [−65–(−39)]	−23 (−86.5–10.5)	0.29
HDL – C	(mg/dl)			
Baseline		46 (43–48)	43.5 (36.25–51)	0.59
6 months		50.63 ± 7.87	47.78 ± 12.61	0.56
Change from baseline		8 (−2–9)	2 (−2.5–1.5)	0.92
LDL – C	(mg/dl)			
Baseline		144 (128–157)	107 (95.75–144.3)	0.16
6 months		141 (111.3–172.5)	113 (92–134)	0.17
Change from baseline		−1 (−42–20)	9 (−25–32)	0.53
HbA1C	(%)	5.52 ± 0.31	5.35 ± 0.50	0.41
Sigstad score				
Baseline		0 (0–0.38)	0 (0–0.5)	0.55
6 months		8 ± 6.3	3.7 ± 3.7	0.09
Change from baseline		7.87 ± 6.25	3.5 ± 3.68	0.08
Arts' score				
Baseline		0 (0–0)	0 (0–0.25)	0.73
6 months		4.5 (3–7.75)	4 (1.75–7.75)	0.92
Change from baseline		4.88 ± 2.7	4.80 ± 3.85	0.96
Early Arts' score				
Baseline		0 (0–0)	(0–0.25)	0.73
6 months		4 (2–6)	3.5 (1–6.75)	0.67
Change from baseline		3.75 ± 1.98	3.90 ± 3.38	0.91
Late Arts' score				
Baseline		0 (0–0)	0 (0–0)	–
6 months		1 (0–2)	0 (0–1.25)	0.39
Change from baseline		1 (0–2)	0 (0–1.25)	0.39

M male, F female, *BMI* body mass index, *EBMIL* excess body mass index loss, *TWL* total weight loss, *HDL – C* high-density lipoprotein cholesterol, *LDL – C* low-density lipoprotein cholesterol

morbidly obese patients who develop or not post-OGTT hypoglycaemia in the early postoperative period after LSG. According to the best of our knowledge, this is the first study which investigates the pathophysiology of hypoglycaemia after LSG.

In the present study, HYPO occurred in 44 % of normoglycaemic obese patients 6 months after LSG. Similarly to our results, Natoudi et al. [6] reported that 37.5 % of NGT subjects developed hypoglycaemia after an OGTT 1 year after LSG. In terms of clinical characteristics, our results suggest that between subjects with NGT, those with HYPO have lower BMI and weight and higher %TWL at 6 months after LSG compared to EU subjects. From metabolic point of view, the most important finding of the present

Table 2 Glucose homeostasis of patients with post-OGTT hypoglycaemia and post-OGTT euglycaemia during the postoperative OGTT

		Hypoglycaemic ($n = 8$)	Euglycaemic ($n = 10$)	p value
Fasting glucose	(mg/dl)			
Baseline		90.50 ± 6.74	94.2 ± 4.42	0.18
6 months		83.38 ± 9.71	87.30 ± 5.27	0.29
Change from baseline		−7.13 ± 7.24	−6.9 ± 3.48	0.93
Glucose AUC (0–120)	(mg/(dl*min))			
Baseline		15,969 ± 2559	15,933 ± 2299	0.98
6 months		12,122 ± 1612	14,252 ± 2282	0.04
Change from baseline		−4050 [−5678–(−2940)]	−2085 (−3518–652.5)	0.03
Glucose AUC (0–30)	(mg/(dl*min))			
Baseline		3611 ± 350.4	3647 ± 348.0	0.69
6 months		3414 ± 517.6	3429 ± 484.4	0.95
Change from baseline		−196.9 ± 345.6	−217.5 ± 388.5	0.91
Glucose AUC (60–120)	(mg/(dl*min))			
Baseline		7821 ± 1517	7826 ± 1316	0.99
6 months		4783 ± 917.3	6638 ± 1321	0.004
Change from baseline		−3038 ± 1627	−1188 ± 1760	0.04
Fasting insulin	(μU/ml)			
Baseline		21.98 ± 12.92	22.17 ± 12.37	0.97
6 months		6.31 ± 2.72	8.00 ± 3.17	0.25
Change from baseline		−15.67 ± 11.75	−14.18 ± 11.28	0.79
Insulin AUC (0–120)	(μU/(ml*min))			
Baseline		13,923 ± 7033	10,840 ± 6609	0.35
6 months		8020 ± 4216	7425 ± 4557	0.78
Change from baseline		−4193 [−7948–(−1901)]	−4083 (−6086–121.3)	0.41
Insulin AUC (0–30)	(μU/(ml*min))			
Baseline		2375 ± 1441	1603 ± 787.9	0.17
6 months		1742 ± 1410	1356 ± 611	0.44
Change from baseline		−633 ± 701.6	−247.1 ± 892.1	0.33
Insulin AUC (60–120)	(μU/(ml*min))			
Baseline		7364 ± 3952	6033 ± 3992	0.49
6 months		2592 (1767–4230)	2513 (1754–4461)	1.00
Change from baseline		−3619 [−5690–(−1910)]	−2177 [−4323–(−880.2)]	0.36
HOMA-IR				
Baseline		4.88 ± 2.84	5.14 ± 2.73	0.85
6 months		1.33 ± 0.67	1.72 ± 0.67	0.23
Change from baseline		−3.55 ± 2.57	−3.41 ± 2.53	0.91
Matsuda index				
Baseline		2.54 (1.17–3.04)	2.27 (1.56–2.74)	0.90
6 months		6.25 (4.06–7.44)	4.69 (3.64–6.68)	0.27
Change from baseline		3.47 (2.27–5.64)	2.33 (1.22–4.25)	0.32
Insulin AUC (0–120)/glucose AUC (0–120)	(μU*dl/(ml*mg))			
Baseline		0.79 (0.44–1.27)	0.59 (0.45–0.88)	0.50
6 months		0.66 ± 0.32	0.50 ± 0.25	0.28
Change from baseline		−0.25 ± 0.40	−0.18 ± 0.34	0.71
Insulin AUC (0–30)/glucose AUC (0–30)	(μU*dl/(ml*mg))			
Baseline		0.55 (0.37–0.89)	0.40 (0.29–0.56)	0.24
6 months		0.51 ± 0.40	0.39 ± 0.16	0.42
Change from baseline		−0.17 ± 0.20	−0.05 ± 0.24	0.29
Insulin AUC (60–120)/glucose AUC (60–120)	(μU*dl/(ml*mg))			
Baseline		0.97 ± 0.56	0.78 ± 0.50	0.45
6 months		0.62 ± 0.21	0.49 ± 0.32	0.34
Change from baseline		−0.40 ± 0.51	−0.29 ± 0.41	0.63
Disposition index AUC (0–120)				
Baseline		1.69 ± 0.52	1.39 ± 0.23	0.12
6 months		3.72 ± 1.33	2.39 ± 0.85	0.02
Change from baseline		2.03 ± 0.97	1.00 ± 0.91	0.03
Disposition index AUC (0–30)				
Baseline		1.27 (0.77–1.75)	0.88 (0.76–1.09)	0.25
6 months		2.77 ± 1.59	2.06 ± 1.25	0.30
Change from baseline		1.50 ± 1.14	1.08 ± 1.15	0.45
Disposition index AUC (60–120)				
Baseline		1.80 ± 0.51	1.52 ± 0.32	0.17
6 months		3.63 ± 1.26	2.10 ± 0.63	0.004
Change from baseline		1.83 ± 1.2	0.58 ± 0.75	0.02

AUC area under the curve, *HOMA-IR* homeostatic model assessment of insulin resistance

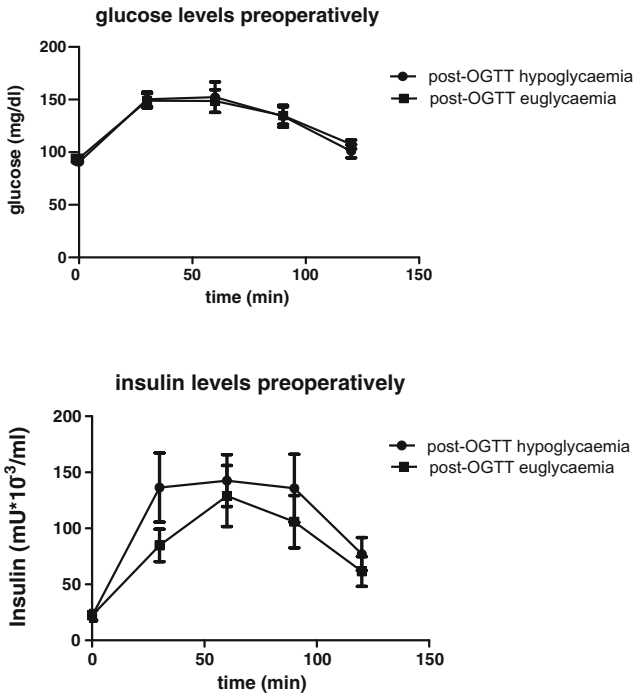

Fig. 1 Glucose and insulin concentrations preoperatively between patients with post-OGTT euglycaemia and post-OGTT hypoglycaemia

study was the higher beta cell function [ODI (0–120)] at 6 months postoperatively at the HYPO group compared to the EU—especially in the latter portion of the OGTT.

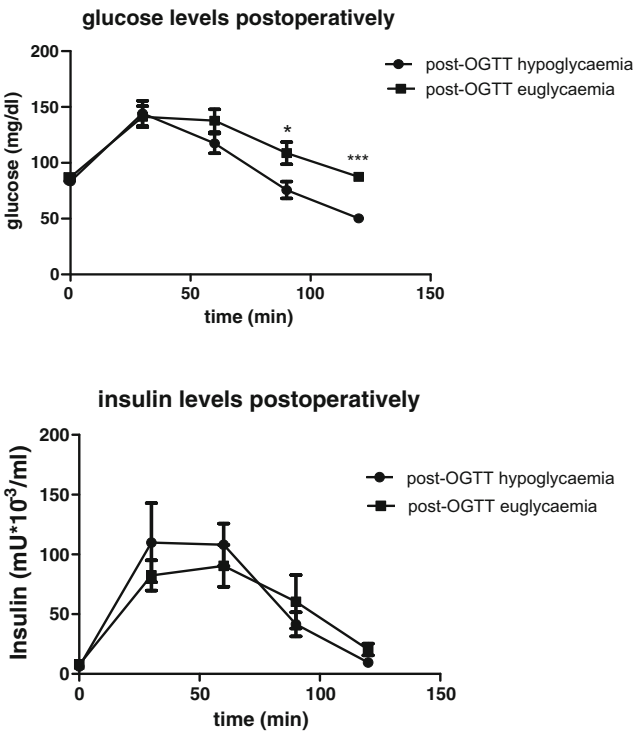

Fig. 2 Glucose and insulin concentrations 6 months after laparoscopic sleeve gastrectomy between patients with post-OGTT euglycaemia and post-OGTT hypoglycaemia $*p < 0.05$, $***p < 0.001$

Other important findings of our study was the trend for lower waist circumference and triglycerides in the HYPO group compared to the EU, suggesting that subjects with less central obesity postoperatively are more likely to develop post-OGTT hypoglycaemia. We also found that subjects who developed HYPO postoperatively had lower preoperative BMI and weight compared to EU. However, the last finding should be interpreted with caution on the basis that the evaluation was in the early postoperative period when both groups had lost exactly the same amount of weight (the change from baseline weight was almost identical for both groups, Table 1) and were still actively losing weight. Thus, it was expected that subjects with the lower postoperative weight and BMI 6 months after LSG will probably have lower weight and BMI preoperatively.

Similar to our study, Itariu et al. [17] investigated subjects without diabetes who developed post-OGTT hypoglycaemia and post-OGTT euglycaemia 1 year after RYGB. They found that younger patients, with lower waist to hip ratio and lower triglycerides, were at higher risk for HYPO postoperatively, but they did not find a difference in BMI or beta cell function postoperatively between the two groups. However, the beta cell function in this study was estimated based on the first phase insulin secretion and this result is consistent with our study's ODI (0–30). The different type of bariatric procedures, the different follow-up, and methodology could explain the different findings between our study and this study. On the other hand, Salehi et al. [25] studied subjects with neuroglycopenic symptoms after RYGB and found that those who developed postprandial hypoglycaemia after a mixed meal test had higher insulin secretion, especially in the latter portion of the meal, and similar insulin sensitivity compared to subjects with postprandial euglycaemia. Moreover, Salehi et al. [25] reported a positive correlation between nadir glucose and BMI, a finding that is in accordance with our results.

Several hypotheses have been suggested to explain the postprandial hypoglycaemia after bariatric operations like RYGB and LSG including (i) the rapid glucose absorption from the gut due to rapid gastric emptying and (ii) the enhanced postoperative beta cell function which could be related with either preoperative or postoperative factors [8, 26–29]. The suggested underlying mechanisms of postprandial hypoglycaemia associated with enhanced beta cell function after bariatric surgery include (i) an increased preoperative beta cell function which does not regress in accordance with the massive weight loss, (ii) the greater insulin action due the increased insulin sensitivity associated with massive weight loss as well as (iii) the enhanced insulin secretion because of increased Glucagon-like peptide-1 (GLP-1) secretion or action [26–29].

The rapid gastric emptying after LSG [30, 31] could result in accelerated entry of carbohydrates into the small intestine with rapid glucose absorption prompting rapid and marked insulin secretion [32]. However, in our study, we did not find differences between the HYPO and EU subjects in the glucose

levels at 30′, peak glucose (data not shown), and glucose AUC (0–30) levels, suggesting that glucose absorption was comparable in these groups. Based on the above findings, it seems less likely that rapid glucose absorption could be the main mechanism of post-OGTT hypoglycaemia after LSG in this study.

On the other hand, despite that the insulin sensitivity and insulin secretion indices were not different between the two groups, the disposition index was significantly higher postoperatively in the HYPO group compared to the EU, suggesting that the higher postoperative beta cell function (adjusted for insulin sensitivity) in the HYPO group could be the underlying mechanism for the postprandial hypoglycaemia after SG.

Multiple factors could be contributed to the higher disposition index in the HYPO group, but the lower BMI and weight, the higher TWL%, and the trend for decreased triglycerides and waist circumference in the HYPO group suggest that the achieved postoperative insulin sensitivity plays an important role. The most likely underlying pathophysiology for this finding is a more disproportionate decrease in insulin secretion to the rise of insulin sensitivity in subjects with HYPO compared to those with EU 6 months after LSG. Indeed, at the present study, the change in insulin secretion from baseline [delta insulin AUC 0–120/glucose AUC (0–120)] was similar at both groups (−17.6 % at HYPO vs −11.9 % at EU, data not shown) despite that the change in insulin sensitivity was almost two times higher in the HYPO group compared to the EU (mean increase at Matsuda index 216.2 % at HYPO group vs 120 % at EU, data not shown) and the baseline insulin secretion in absolute numbers was also higher for the HYPO group (Table 2).

Previous studies in obese subjects after significant weight loss with bariatric procedures have reported an increased disposition index after the intervention compared to baseline which in the majority of the cases was proportionate to the achieved BMI [33, 34]. Indeed, a negative correlation between the ODI (60–120) and the postoperative weight and BMI was identified in our study, suggesting that the lower is the weight and the BMI the higher is the late disposition index. Additionally, the trend towards decreased triglycerides and waist circumference in the HYPO group postoperatively compared to the EU group suggests that patients in the HYPO group may have lower amounts of abdominal fat postoperatively which could result in decreased free fatty acids and lipotoxicity and consequent increased beta cell function postoperatively [33].

The elevated GLP-1 levels after LSG [35] could also be contributed in the increased beta cell function postoperatively, but whether there is a difference in GLP-1 levels and action between HYPO and EU group and whether this could result in increased beta cell function in the HYPO group after LSG needs further investigation.

In our study, the HYPO group did not have significantly different beta cell function preoperatively compared to the EU group [ODI (0–120) ($p = 0.12$)]. This is not surprising, considering that all the patients were NGT; however, further studies will be needed to confirm this finding.

HYPO group had a trend to report more dumping symptoms compared to the EU group but symptoms of late dumping—which are related with hypoglycaemia—were almost identical between the two groups postoperatively, and the majority of patients with HYPO had mild hypoglycaemic symptoms or were asymptomatic. Although severe hypoglycaemia after bariatric procedures can lead to dangerous clinical consequences such as seizure, syncope, and motor vehicle accidents, the clinical relevance of mild or asymptomatic hypoglycaemia is less clear [8, 26]. It has been suggested that hypoglycaemia after bariatric surgery might contribute to the increased risk of death from non-disease related causes, such as accidental deaths and suicide [36, 37], as hypoglycaemia is known to determine an increase in depressive symptoms [17, 38]. Hence, these patients could suffer from hypoglycaemia-related impairments of cognitive and motor functions without being aware of it [17, 39]. Therefore, being able to identify early patients at high risk for postprandial hypoglycaemia and to provide them with specific diet instructions could be of high importance. Our findings suggest that patients with BMI lower than 29 kg/m^2 6 months after LSG are at high risk for developing post-OGTT hypoglycaemia, and these patients may benefit from specific dietetic advice on how to avoid postprandial hypoglycaemia in their daily life. It is also likely that patients with post-OGTT euglycaemia at 6 months after LSG will develop post-OGTT hypoglycaemia if they improve further their insulin sensitivity through further weight loss. However, longer follow-up of the patients is necessary to confirm this hypothesis.

We are aware of some limitations of our study; the number of patients included was small, we did not measure c-peptide, glucagon, incretin levels [GLP-1, Gastric inhibitory peptide (GIP)], and gastric emptying which all could contribute to glucose homeostasis, and we used empirical indices derived from the OGTT in order to calculate beta cell function. Furthermore, the 6-month follow-up could obscure several cases of hyperinsulinaemic hypoglycaemia which often occurs after the first six postoperative months. Finally, the insulin clearance that could be contributed in the post-OGTT hypoglycaemia after LSG have not been investigated in this study; however, it has been shown that postprandial insulin clearance remain unchanged in patients with NGT after bariatric surgery [40].

Conclusion

In summary, we report herein that NGT subjects with HYPO 6 months after LSG have lower BMI and weight, higher %TWL, and increased beta cell function postoperatively—especially in the latter portion of the OGTT—compared to

subjects with EU. Further long-term studies on the preoperative and postoperative anthropometrics, islet function, and insulin sensitivity in patients with postprandial hypoglycaemia after LSG are necessary in order to understand better the pathophysiology of this phenomenon. This may allow us to identify early patients with high risk for postprandial hypoglycaemia, and to develop further treatment options for this complication.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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