https://doi.org/10.31925/farmacia.2022.4.13 **ORIGINAL ARTICLE**

INFLUENCE OF TYPE 2 DIABETES ON THE ANTHROPOMETRIC INDICES, BODY COMPOSITION AND MICRONUTRIENT STATUS OF PATIENTS SUBMITTED TO LAPAROSCOPIC SLEEVE GASTRECTOMY

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Abstract

The objectives of this study were to determine whether or not the presence type 2 diabetes (T2D) is associated with significantly less postoperative weight loss and to evaluate the impact of T2D on body composition and micronutrient status in patients submitted to laparoscopic sleeve gastrectomy (LSG). The study was conducted on 50 men and women (12 with T2D) that were evaluated preoperatively and at 6 and 12 months following LSG. Patients with T2D lost significantly less weight and visceral fat at 12 months following LSG compared with their counterparts without T2D, despite comparable BMI at baseline. Also, patients with T2D exhibited a significantly higher fat-free mass at the end of the follow-up period (but also lost less weight), although the total fat mass loss did not differ significantly between patients with and without T2D both pre- and postoperatively. 25(OH) D deficiency was present in all patients in baseline and this abnormality persisted throughout the follow-up period, irrespective of T2D status and routine nutritional supplementation; vitamin B_{12} serum levels were significantly higher (but keeping within the normal range) in the T2D group pre- and post-LSG. T2D negatively impacts both weight loss and body composition improvement following LSG. Except for vitamin B_{12}, micronutrient levels evaluated herein were comparable between the two groups.

Rezumat

Obiectivele acestui studiu au fost de a determina dacă prezența diabetului de tip 2 (DZ2) este sau nu asociată cu o pierdere semnificativ mai mică în greutate după intervenția de *sleeve* gastrectomie laparoscopică (SGL) și de a evalua impactul DZ2 asupra compoziției corporale și a profilului de micronutrienți în rândul pacienților supuși SGL. Studiul a fost realizat pe 50 de bărbați și femei (din care 12 au fost diagnosticați cu DZ2 preoperator) care au fost evaluați preoperator și la 6, respectiv 12 luni, după SGL. Pacienții cu DZ2 au înregistrat o reducere ponderală semnificativ mai mică și au pierdut mai puțină grăsime viscerală la 12 luni după SGL în comparație cu pacienții fără DZ2, în ciuda unui indice de masă corporală comparabil la momentul preoperator. De asemenea, nivelul masei slabe a fost semnificativ mai mare la sfârșitul perioadei de follow-up în rândul pacienților cu DZ2 față de cei fără DZ2 (dar, în același timp, primii au pierdut mai puțin în greutate). Nivelul masei grase nu a diferit în mod semnificativ între pacienții cu și fără DZ2 nici înainte, nici după intervenția de SGL. Deficitul de 25(OH) D a fost prezent la toți pacienții preoperator, această carență persistând pe toată perioada de *follow-up*, indiferent de prezența DZ2 și în ciuda suplimentării nutriționale; nivelurile serice ale vitaminei B_{12} au fost semnificativ mai mari (dar în limitele intervalului de referință) în grupul pacienților cu DZ2 atât pre-, cât și postoperator. DZ2 este asociat cu efecte negative în ceea ce privește reducerea ponderală și ameliorarea compoziției corporale după SGL. Cu excepția vitaminei B_{12}, nivelurile micronutrienților investigați în acest studiu au fost comparabile între cele două grupuri de pacienți.

Keywords: type 2 diabetes, laparoscopic sleeve gastrectomy, body composition, micronutrient status

Introduction

The rising burden of type 2 diabetes (T2D) is a major health threat worldwide [1]. Certain bariatric procedures (*e.g.*, laparoscopic Roux-en-Y gastric bypass, LRYGB, or laparoscopic sleeve gastrectomy, LSG) have been shown to produce durable improvement of T2D, restoring glycaemic control in the early postoperative

period through weight-loss independent mechanisms [2]. Thus, the use of such procedures to treat T2D *per se* rather than obesity has increased in recent years as multiple international diabetes and surgery societies recommend these interventions in non-morbidly obese patients with poorly controlled T2D and a body mass index (BMI) as low as 30 kg/m^2 [3]. Moreover, the term "metabolic" is nowadays included in the names of the most bariatric surgical organizations worldwide [2].

The individual response to weight loss after bariatric surgery (BS) is highly variable [4, 5]. Several factors affect weight outcomes, such as baseline BMI, age, sex, preoperative weight loss, eating behaviour, tobacco use, substance abuse or the presence of T2D. The latter has been proven to be one of the most important factors those impacts on the likelihood of effectively losing weight following BS [4]. Luo *et al*. analysed retrospectively collected data from 714 adult patients enrolled in The Michigan Bariatric Surgery Cohort that underwent either LRYGB (n = 380; 80.3% women) or LSG (n = 334; 77.5% women) showing that individuals with T2D were significantly less likely to achieve an excess body weight loss ≥ 50% and lost fewer BMI points, irrespective of surgery type, compared with individuals without T2D. Moreover, in linear mixed models analysis adjusted for surgery type, baseline weight, age and sex, individuals with T2D had lower absolute weight loss, percentage of total weight loss (%TWL) and excess weight loss (%EWL) *versus* individuals without T2D over 5 years of follow-up [6]. While weight loss is commonly used as an indicator of "success" following BS, the change in the BMI do not mirror the changes in body composition (BC) components, termed fat mass (FM) [7] and fat free mass (FFM). BC improvement after BS entails lowering of FM, particularly the visceral fat compartment, and preservation of FFM [4]. BC postoperative accurate evaluation is important in terms of both weight loss and obesity-related comorbidities. Firstly, given that FFM, the main metabolically active tissue, is a key component of the energy expenditure, a reduction in lean mass could hamper weight loss [7]. Secondly, it is suggested that adipose tissue components rather than weight loss *per se* significantly impacts the obesity-related metabolic diseases [4].

Micronutrients are important for optimal metabolic function. Certain micronutrients are involved in insulin signalling cascade, β-cell function or play key roles as cofactors in multiple glucose biochemical pathways, suggesting that they might influence the development of T2D [8]. For example, vitamin D receptor is expressed in many cells, including muscular, adipose, hepatic and pancreatic β-cells [9]. Vitamin D deficiency is related to insulin resistance, reduced insulin secretion and T2D development. Altered glycaemic control and T2D may also be the result of certain genetic polymorphisms of vitamin D-related genes. Evidence from epidemiological studies indicate an association between low levels of circulating 25-hydroxivitamin D and T2D or metabolic syndrome, partly due to increased fat mass [10]. Other micronutrients commonly deficient in T2D patients are folate [11] and vitamin B_{12} [12] whose absorption is impaired due to prolonged use of metformin [11]. In addition, despite its effectiveness in terms of weight loss and comorbidities resolution, including T2D, LSG is also associated with the development of micronutrient deficiencies (MNDs), among which vitamin D, vitamin B_{12}, folates and iron are the most prevalent [13, 14].

Although several studies have investigated the influence of T2D upon weight loss response after LSG, data concerning the impact of T2D on the trajectory of changes in BC as well as in the micronutrient status following BS is scarce.

Our purpose was i) to determine the impact of T2D on postoperative weight loss, ii) to evaluate the effects of T2D status on BC compartments (FM, including visceral fat, and FFM) and iii) to assess the effects of T2D upon micronutrient status before and at 6 and 12 months after LSG.

Materials and Methods

Patients and study design

Fifty patients with severe obesity who underwent LSG as a single procedure at the Ponderas Academic Hospital, Romania, between 2014 and 2015 were enrolled in this observational longitudinal study with retrospective and prospective data collection. All patients met the eligibility criteria for BS [15] with a BMI of ≥ 40 kg/m^2 without existing comorbidities or a BMI between 35 and 40 kg/m^2 with at least one severe obesity-associated disease. Patients were followed-up at 6 and 12 months, respectively, after LSG.

All participants provided informed consent prior to study enrolment. Each procedure involving human subjects complied with the hospital research committee and the 1964 Declaration of Helsinki ethical standards. The study was approved by the Ethics Committee.

Pre- and postoperative assessment

Pre- and postoperative assessment at 6 and 12 months was performed by a multidisciplinary team, according to international guidelines [16]. Medical history was recorded and anthropometrical, nutritional and biochemical evaluations were performed at all time points of the study. Medical history is reported in Table VIII. Dyslipidaemia was defined as LDL-c ≥ 100 mg/dL, HDL-c < 45 mg/dL in men and < 55 mg/dL in women, triglyceride > 150 mg/dL or as the use of anti-dyslipidaemic medication. Hypertension was defined as sistolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg or the use of antihypertensive medication. Non-alcoholic fatty liver disease (NAFLD) diagnosis was determined by performing ultrasonography.

Height and weight were measured at baseline and at each postoperative visit. Height was determined using a wall-mounted stadiometer, while weight was measured with a calibrated scale. BMI was determined as weight divided by height squared. Waist and hip circumference (WC, HC) were evaluated according to standardized procedures at the umbilical and the greater trochanter level, using a flexible measuring tape. Two repeated measurements were performed at each site level. Consecutively, all patients were scanned on the iDXA (GE Healthcare, Madison, WI, USA) by a technician using standardized procedures recommended by the manufacturer. Variables of interest from the CoreScan software scans included fat-free mass (FFM) expressed in kg, fat mass expressed as percentage of total body fat (FM%) and visceral adipose tissue mass within the android region expressed in grams (VATg) and percentage (VAT%).

Weight loss was assessed according to the excess weight loss (%EWL) and total weight loss (%TWL) formulas:

$$\%EWL = [(\text{initial weight-postop weight})/(\text{initial weight-ideal weight*})] \times 100,$$

where, *ideal body weight = the weight corresponding to a BMI of 25 kg/m^2;

$$\%TWL = [(\text{initial weight-postop weight})/\text{initial weight})] \times 100 \text{ [17].}$$

Blood samples were collected after a 12-h overnight fast both preoperatively and at 6 and months post-operatively. The blood assays were performed immediately after centrifugation or otherwise the samples were stored at -80ºC until the corresponding tests were run. Metabolic and nutritional parameters evaluated in this study and were fasting blood glucose (FPG), HbA_{1c}, 25(OH) D, vitamin B_{12}, folate, serum iron and ferritin. Excepting serum micronutrient concentration for vitamins and minerals that were assessed at Biogen Medical Laboratory Cluj-Napoca, Romania, all other parameters and measurements were determined at the hospital's facilities.

Criteria used to define T2D were based on the American Diabetes Association guidelines [18], whereas remission criteria for T2D were considered as follows: (i) total remission: a return to normal biological values of glucose metabolism, respectively FPG < 100 mg/dL (≤ 5.6 mmol/L), and/or $HbA_{1C} \leq 6\%$ (42 mmol/mol)) in the absence of antidiabetic medications; (ii) partial remission: sub-diabetic hyperglycaemia (FPG 100 - 125 mg/dL) in the absence of antidiabetic medications [17]. Deficiency in a vitamin or mineral was considered if the serum concentration of the respective micronutrient was below the reference range. 25(OH)D status was categorized was categorized depending on its serum levels as follows: deficient if < 10 ng/mL, insufficient if between 10 and 29 ng/mL and optimal if > 30 ng/mL; vitamin B_{12} deficiency was defined as < 193 pg/mL and folate deficiency as < 2.7 ng/mL; iron deficiency was defined as serum iron < 50 μg/dL or ferritin < 28 ng/mL in male and < 5 ng/mL in female.

Nutritional assessment and counselling

Nutritional assessment was performed by a specialized multidisciplinary team at baseline and at the follow-up visits. Routine dietary recommendations and counselling were provided at each appointment. Nutritional supplementation was indicated in all patients after LSG following the same protocol: 1 multivitamin and mineral tablet daily during the first year plus daily oral calcium citrate (500 mg), iron (28 mg), vitamin D (2000 IU) and B_{12} (1000 μg) along the first 3 months postoperatively.

Surgical technique

The surgical technique of LSG was performed as previously described [19].

Statistical analysis

Statistical analyses were performed using SPSS version 19.0. Data were tested for normality using the Kolmogorov-Smirnov tests. Continuous variables were described as means and standard deviations, respectively median for not normally distributed data, while categorical variables were expressed as absolute numbers and proportions. Means within same group were compared using ANOVA test with repeated measures for normally distributed data and, respectively, Friedman test for non-normally distributed variables. Student's *t* test was applied to assess comparisons between groups for normally distributed data, whereas Mann-Whitney test was used if data followed a non-normal distribution. A p-value less than 0.05 was considered statistically significant.

Results and Discussion

Baseline characteristics of patients with and without T2D before undergoing LSG are described in Table I and Table II. Patients with T2D (n = 12) were mostly women (male-to-female ratio of 1:1.4), with a mean (standard deviation) age of 53.7 (10.0) years, a mean BMI of 44.2 (5.8) kg/m^2, a mean FPG of 158.5 (129 - 199.5) mg/dL and a mean HbA_{1c} of 7.6% (1.2%). Patients without T2D (n = 38) were also mostly women (male-to-female ratio of 1:2.7), significantly younger (44.2 (10.1) years) than their T2D counterparts, but with a comparable BMI (43.1 (5.6) kg/m^2). No statistically significant differences were observed regarding WC, HC between the T2D and the non-T2D group in baseline (p = 0.152 and p = 0.131). Also, the T2D group did not exhibit a significantly higher FFM, FM or abdominal fat mass (expressed as VAT%) compared to their non-T2D counterparts before surgery. Roughly 2/3 of patients from both groups suffered from severe obesity (class III) before undergoing LSG. The baseline rate of comorbidities (dyslipidaemia, hypertension and NAFLD) was not significantly different between the two groups with one exception, hypertension, which was significantly higher among the T2D patients (p = 0.047) (Table II).

Table I

Characteristics of study participants with and without T2D before LSG

(n = 50)	T2D (n = 12)	Without T2D (n = 38)	p value
Female n (%)	7 (58)	26 (68)	0.999
Age (years)	53.7 (10.0)	44.2 (10.1)	0.007*
Weight (kg)	128.0 (23.0)	115.7 (107.8 - 131)	0.388
BMI (kg/m^2)	44.2 (5.8)	43.1 (5.6)	0.556
WC (cm)	133.8 (14.9)	124.5 (120 - 139)	0.152
HC (cm)	138.5 (12.4)	130.5 (123.75 - 138.5)	0.131
FFM (kg)	63.3 (12.2)	50.0 (46.0 - 60.6)	0.256
FM (%)	50.0 (4.0)	52.7 (46.9 - 55.7)	0.241
VAT (g)	4337.4 (1734.9)	2796.2 (1187.44)	0.140
VAT (%)	6.9 (2.4)	5.0 (1.8)	0.440
Fasting plasma glucose (mg/dL)	158.5 (129 - 199.5)	95.6 (13.6)	< 0.005*
HbA_{1c} (%)	7.6 (1.2)	-	-

*indicates a statistically significant result

Table II

Baseline comorbidities of participants with and without T2D before LSG

(n = 50)	T2D (n = 12)	Without T2D (n = 38)	p value
History of obesity (years)	16.7 (12.3)	16.3 (9.3)	0.844
Obesity class III n (%)	9 (75)	27 (71)	0.791
Dyslipidaemia n (%)	9 (75)	31 (82)	0.619
Hypertension n (%)	9 (75)	16 (42)	0.047*
NAFLD n (%)	11 (92)	31 (82)	0.553

*indicates a statistically significant result

A significant decrease in BMI was documented at 6 and 12 months compared to baseline within the T2D group ($p \leq 0.001$), but not from 6 months to 12 months ($p = 0.361$). Also, a significant reduction in WC, HC and FM% was observed at the first follow-up (6 months postoperatively) compared to the pre-operative period, but these differences did not persist between 6 months to 12 months postoperatively (the second follow-up point). FFM decreased significantly from baseline to 6 and 12 months postoperatively. No statistically significant differences between baseline, 6- and 12- months post-LSG were observed for VAT%. %EWL and %TWL did not increase significantly between the first and the second follow-up points (Table III).

Table III

Anthropometric, body composition and weight loss parameters of study participants with T2D before and after LSG

Outcome	Baseline		6 months		12 months		p value
	Results	n/100%	Results	n/100%	Results	n/100%	-
Weight (kg)	128.0 (23.0)	12/100	96.2 (15.7)*	12/100	92.3 (14.4)*	12/100	< 0.001
BMI (kg/m^2)	44.2 (5.8)	12/100	33.6 (4.4)*	12/100	31.6 (3.8)*	12/100	< 0.001
WC (cm)	133.7 (14.9)	12/100	111.3 (10.4)*	12/100	107 (11.1)*	12/100	< 0.001
HC (cm)	138.5 (12.4)	12/100	109 (108 - 113)*	12/100	111.2 (109.5)*	12/100	0.002
FFM (kg)	63.3 (12.2)	9/75	54.3 (10.9)*	10/83	54.7 (11.1)*	9/75	0.009
FM (%)	50.0 (4.0)	8/67	35.8 (6.8)*	10/83	41.6 (34.35 - 43.7)*	9/75	0.002
VAT (g)	4337.4 (1734.9)	7/58	2014.7 (1155.5)	10/83	1673.6 (1005.5)	9/75	0.002
VAT (%)	6.9 (2.4)	7/58	6.0 (2.9)	10/83	4.8 (2.5)	9/75	0.403
EWL (%)	-	-	59.5 (15.9)	12/100	68.0 (16.3)	11/92	0.110
TWL (%)	-	-	24.6 (5.6)	12/100	28.6 (5.6)	11/92	0.091

*indicates a statistically significant result ($p < 0.05$) compared to baseline

In the non-T2D group, significant differences for BMI, WC, HC, FM% were observed between each evaluation (baseline to 6 and 12 months and 6 to 12 months postoperatively). There was a significant decrease in FFM between baseline and the second follow-up ($p = 0.016$) as well as between the first and the second evaluation ($p = 0.009$), but not after 6 months following surgery ($p = 0.833$). VAT% changed significantly between baseline and 6, respectively 12 months, but not between the first and the second follow-up ($p = 0.508$). Significant differences between 6- and 12-months postoperatively were observed for %EWL and %TWL (Table IV).

Table IV

Anthropometric, body composition and weight loss parameters of study participants without T2D before and after LSG

Outcome	Baseline		6 months		12 months		p value
	Results	n/100%	Results	n/100%	Results	n/100%	-
Weight (kg)	115.7 (107.7 - 131)	38/100	82.5 (73.9 - 93.5)*	38/100	72.5 (64.7 - 86.5)* **	38/100	< 0.001
BMI (kg/m^2)	43.1 (5,58)	38/100	30.3 (4.19)*	38/100	26.3 (24.6 - 28.9)* **	38/100	< 0.001
WC (cm)	124.5 (120 - 139)	38/100	101.3 (12.04)*	38/100	92.5 (85.7 - 100.7)* **	38/100	< 0.001
HC (cm)	130.5 (123.7 - 138.5)	38/100	106 (101.7 - 112.2)*	38/100	101 (94.7 - 108)* **	38/100	< 0.001
FFM (kg)	50.0 (46.0 - 60.5)	22/58	48.9 (41.3 - 59.7)	36/95	44.5 (40.5 - 57.1)*	30/79	0.016
FM (%)	52.7 (46.9 - 55.7)	22/58	39.8 ± 9.21*	35/92	35.8 (27.7 - 42.2)* **	30/79	< 0.001
VAT (g)	2796.2 (1187.4)	21/55	1259.9 (551.3)	35/92	785.6 (422.7)	29/76	< 0.001
VAT (%)	5.0 (1.8)	21/55	2.5 (1.1)*	35/92	2.9 (1.2)*	29/76	< 0.001
EWL (%)	115.7 (107.7 - 131)	-	73.6 (63.8 - 81.2)	38/100	91.7 (16.9)	34/89	< 0.001
TWL (%)	43.1 (5,58)	-	29.5 (5.0)	38/100	37.0 (6.0)	34/89	< 0.001

*indicates a statistically significant result ($p < 0.05$) compared to baseline; ** indicates a statistically significant result ($p < 0.05$) compared to previous measurement

FPG was significantly lower between baseline and the first and, respectively, between baseline and the second follow-up, but not between the first and the second follow-up points ($p = 0.456$) (Figure 1).

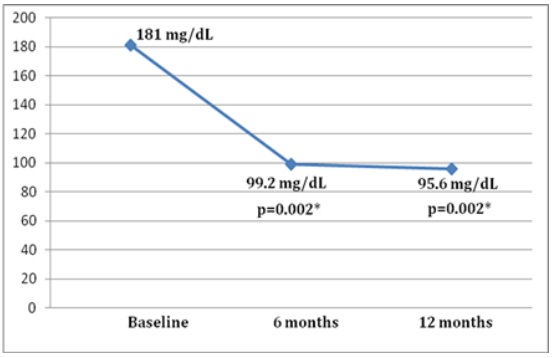

Figure 1.

Trajectory of glycaemic levels throughout the study follow-up

*indicates a statistically significant result ($p < 0.05$) compared to baseline

24% of the cohort included in the present study suffered from T2D in baseline. Despite lower weight loss and less improvement in BC compartments, 50% (n = 6) and, respectively, 58% (n = 7) of patients met the criteria for complete T2D remission at 6- and 12- months post-LSG (Table V).

Table V

Remission of T2D after LSG

(n = 12)	6 months	12 months	p value
Total remission n (%)	6 (50%)	7 (58%)	NA
Partial remission n (%)	4 (33%)	4 (33%)	NA

NA = not available

Partial remission of T2D was also observed in 33% of patients at both follow-up points. No statistically significant differences between baseline, 6- and 12-months postoperatively were documented within the T2D group and the non-T2D group for 25(OH)D, vitamin B_{12}, folate, serum iron and ferritin levels (Table VI and Table VII).

Table VI

Micronutrient parameters of study participants with T2D before and after 6- and 12- months following LSG

Outcome	Baseline		6 months		12 months		p value
	Results	n/100%	Results	n/100%	Results	n/100%	-
25(OH)D (ng/mL)	9.2 (2.3)	6/50	10.8 (9.8 - 12.7)	12/100	11.6 (5.4)	7/58	0.846
B_{12} (pg/mL)	433.3 (231.9)	12/100	434.2 (210.9)	12/100	475.2 (190.9)	12/100	0.779
Folate (ng/mL)	6.1 (5.2 - 7.3)	12/100	11.2 (6.7)	12/100	5.8 (3.7 - 10.3)	12/100	0.105
Serum iron (µg/dL)	71.0 (25.5)	12/100	95.0 (42.0)	12/100	96.8 (33.1)	10/83	0.326
Ferritin (ng/mL)	183.7 (187.0)	7/58	182.2 (155.6)	12/100	111.2 (65.2)	9/75	0.435

Table VII

Micronutrient parameters of study participants without T2D before and after 6- and 12- months following LSG

Outcome	Baseline		6 months		12 months		p value
	Results	n/100%	Results	n/100%	Results	n/100%	-
25(OH)D (ng/mL)	9.8 (2.5)	18/47	9.5 (8.5 - 11.9)	37/97	10.2 (8.4 - 12.9)	31/82	0.211
B_{12} (pg/mL)	290.1 (215.2 - 377.2)	12/100	283.5 (225.7 - 360)	12/100	283.2 (209.0 - 339.0)	36/95	0.920
Folate (ng/mL)	5.8 (4.5 - 7.6)	12/100	5.1 (3.8 - 9.9)	12/100	4.0 (3.0 - 9.2)	33/87	0.564
Serum iron (µg/dL)	94.8 (34.4)	37/97	98.6 (31.7)	12/100	111.9 (39.9)	35/92	0.075
Ferritin (ng/mL)	170.0 (88.3)	18/47	128 (78.2 - 209.5)	37/97	133.0 (87.3)	31/82	0.703

Weight loss and improvement in anthropometric and body composition parameters were noticed in both groups at 6- and 12- months after LSG. However, weight loss profile (Figure 2) significantly differed at the first and second follow-up points according to T2D status.

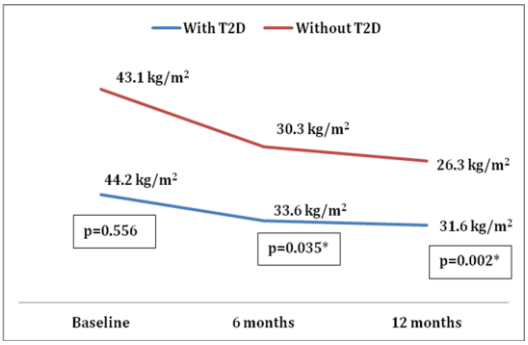

Figure 2.
Evolution of BMI before and after 6 and 12 months following LSG in patients with T2D and without T2D
*indicates a statistically significant result ($p < 0.05$)

As such, weight loss expressed as %TWL was significantly lower in the T2D group *versus* the non-T2D group at 6- and 12- months post-LSG (Figure 3). WC was significantly lower at 6- and 12- months following LSG in the non-T2D group compared to the T2D group ($p = 0.016$ and $p = 0.006$).

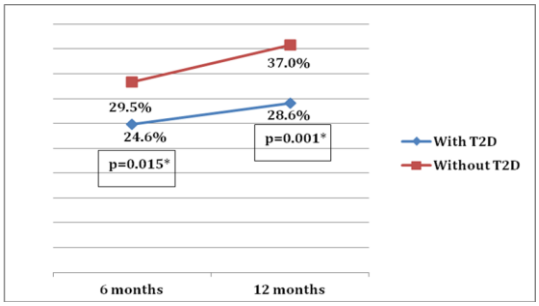

Figure 3.
Trajectory of %TWL after 6 and 12 months following LSG in patients with T2D and without T2D
*indicates a statistically significant result ($p < 0.05$)

HC differed significantly between the two groups only at the second follow-up up point, when it was also significantly lower in the non-T2D group ($p = 0.005$). FFM was significantly higher among patients with T2D at 12 months post-LSG compared with patients without T2D (Figure 4).
No significant differences between groups were observed at 6- and 12 months postoperatively concerning total FM loss (Figure 5). However, android fat mass expressed as VAT% differed significantly between the two groups at both 6- and 12- months postoperatively, remaining higher in the T2D group (Figure 6).

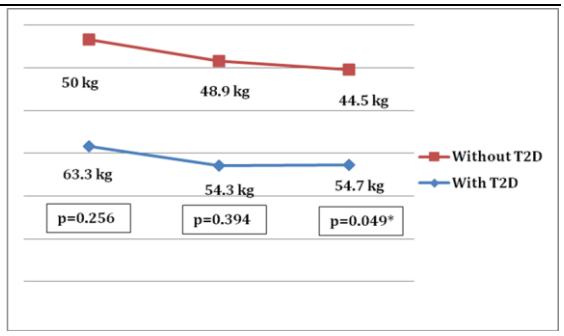

Figure 4.
FFM in baseline and its trajectory throughout the study follow-up between patients with and without T2D
*indicates a statistically significant result ($p < 0.05$)

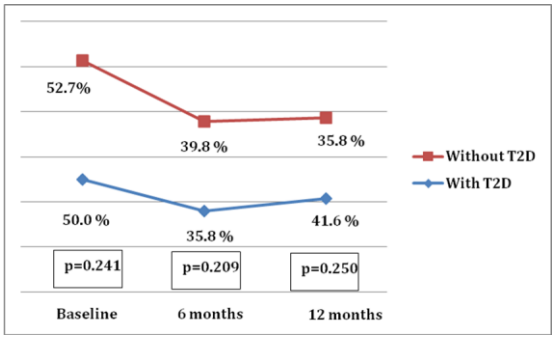

Figure 5.
FM% in baseline and its trajectory throughout the study follow-up between patients with and without T2D
*indicates a statistically significant result ($p < 0.05$)

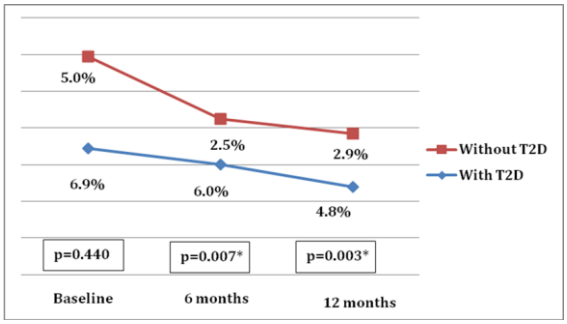

Figure 6.
VAT% in baseline and its trajectory throughout the study follow-up between patients with and without T2D
*indicates a statistically significant result ($p < 0.05$)

25(OH)D deficiency was diagnosed in all patients in baseline, irrespective of T2D status. In the T2D group, vitamin D remained insufficient at both follow-up points. Among non-T2D patients, vitamin D deficiency persisted at 6 months and slightly increased at 12 months following LSG (Figure 7). Except for vitamin B_{12}, whose levels were higher pre- and postoperatively among T2D patients *versus* non-T2D patients (Figure 8), no significantly differences between the two groups were observed at baseline and to 6- and 12- months

post-LSG with regard to micronutrient levels followed in this study (Table VIII and Table IX).

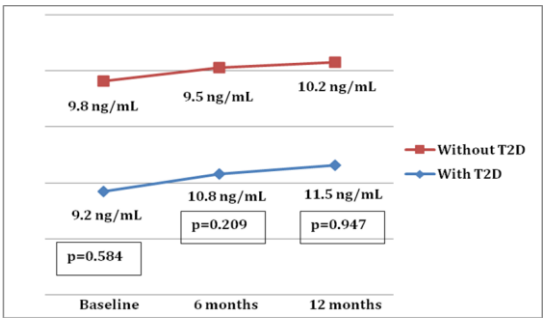

Figure 7.
25(OH)D concentration in baseline and its trajectory throughout the study follow-up between patients with and without T2D

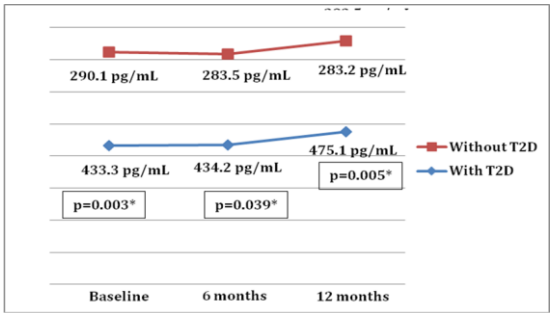

Figure 8.
Vitamin B_{12} concentration in baseline and its trajectory throughout the study follow-up between patients with and without T2D
*indicates a statistically significant result ($p < 0.05$)

Table VIII
Comparison of anthropometric, body composition, weight loss and nutritional parameters in patients with T2D and without T2D 6 months after LSG

Outcome	T2D	Without T2D	p value
Weight (kg)	96.2 (15.8)	82.5 (73.9 - 93.5)	0.012*
WC (cm)	111.3 (10.4)	101.3 (12.0)	0.016*
HC (cm)	109 (108 - 113)	106 (101.7 - 112.2)	0.127
VAT (g)	2014.7 ± 1155.5	1259.9 (551.3)	0.006*
EWL (%)	59.5 (15.9)	73.6 (63.8 - 81.3)	0.018*
Folate (ng/mL)	11.2 (6.7)	5.1 (3.8 - 9.9)	0.084
Serum iron (µg/dL)	95.0 (42.0)	98.6 (31.7)	0.754
Ferritin (ng/mL)	182.2 (155.6)	128 (78.2 - 209.5)	0.798

*indicates a statistically significant result ($p < 0.05$)

Table IX
Comparison of anthropometric, body composition, weight loss and nutritional parameters in patients with T2D and without T2D 12 months after LSG

Outcome	T2D	Without T2D	p value
Weight (kg)	92.3 (14.3)	72.5 (64.7 - 86.5)	0.005*
WC (cm)	107.0 (11.1)	92.5 (85.7 - 100.7)	0.006*
HC (cm)	111.2 (109.5)	101 (94.7 - 108)	0.005*
VAT (g)	1673.6 (1005.5)	785.6 (422.6)	< 0.001*
EWL (%)	68.0 (16.3)	91.6 (16.9)	< 0.001*
Folate (ng/mL)	5.82 (3.7 - 10.3)	4.0 (3.0 - 9.2)	0.238
Serum iron (µg/dL)	96.8 (33.1)	111.9 (39.9)	0.281
Ferritin (ng/mL)	111.2 (65.2)	133.0 (87.4)	0.734

*indicates a statistically significant result ($p < 0.05$)

The main findings of the study are: i) T2D negatively impacts both weight loss and body composition parameters in patients submitted to LSG; patients with T2D lost significantly less weight and visceral fat (VAT%) and maintained a higher WC compared with their counterparts without T2D, despite comparable BMI at baseline; ii) with regard to BC, patients with T2D exhibited a significantly higher FFM at the end of the follow-up period (but also lost less weight), although the total FM% loss did not differ significantly between patients with and without T2D both pre- and post-operatively; iii) 25(OH) D deficiency was present in all patients in baseline and this abnormality persisted throughout the follow-up period, irrespective of T2D status; no significant differences were found between the two groups concerning the micronutrient status except for vitamin B_{12}, whose serum levels were significantly higher in the T2D group pre- and post-LSG.

To our best knowledge, so far only one study assessed whether and how T2D status influence both weight loss and BC parameters assessed by DXA post-LSG [4]. Regarding overall weight loss (in both groups), in our sample TWL% ranged between 28 and 37 at 1 year, indicating the efficacy of LSG in reducing weight irrespective of T2D status. However, when compared to their non-T2D counterparts, patients with T2D did exhibit lower weight loss at 1 year following LSG.

This finding is consistent with those described by Diedisheim *et al*., who investigated the impact of T2D on weight loss status and BC in 373 patients submitted to LSG (of which 40% had T2D). Patients with T2D lost less weight at 1 year than patients without T2D (21 *versus* 27% from baseline, $p < 0.001$) [4]. In our sample, we noticed a higher weight loss in T2D individuals at 1 year, respectively 28% from baseline (%TWL), but compared to the weight loss of patients without T2D (%TWL = 37) it was significantly lower ($p \leq 0.001$). These results suggest that optimizing glycaemic control before BS might be a reasonable approach to attain better weight loss outcomes in T2D patients submitted to LSG [4].

Factors associated with weight loss response in T2D patients have not been very well defined following LSG, although they have been studied extensively after LRYGB [20, 21]. In these patients weight loss following BS may be prevented by several factors, including medication to treat T2D, increased caloric intake in order to avoid hypoglycaemic episodes, reduced glycosuria as well as insulin-induced renal retention of water and sodium [22]. Although it induces marked improvement in glycaemic regulation, antidiabetic medication (insulin therapy with or without insulin secretagogues) determines weight gain and subsequent worsening of insulin resistance. In other words, the efforts to optimize glycaemic control interfere with the efforts to reduce weight, creating a vicious cycle [20]. Indeed, studies assessing either conventional or surgical treatment for obesity (BS) have suggested that the presence of T2D is associated with poor postoperative weight loss. A study investigating the effects of a 20-week behavioural weight-control program on individuals with T2D and their spouses without T2D found out that the latter lost significantly more weight [23]. In a cohort consisting of 3193 patients of which 20% had T2D, Carbonell *et al*. showed that the magnitude of weight loss was significantly lower in patients with T2D compared to their non-T2D counterparts 1 year after BS. In addition to the afore-mentioned factors related to T2D and its treatment, in BS studies poorer response to weight loss after BS in patients with T2D was also shown to be influenced by preoperative weight, age or unfavourable metabolic profile (more comorbidities). Since the severity of T2D is associated with preoperative weight and BMI, greater preoperative weight was thought to be related to worse postoperative weight trajectories following BS [20]. Previous studies have shown that a greater preoperative weight is associated with lower %EWL after BS [24]. However, %EWL does not necessarily accurately reflect postoperative weight loss because patients with lower weight also have lower excess weight; therefore, when they lose weight, even in small amounts, their %EWL will be higher. This is the reason why many authors recommend assessing %TWL instead of %EWL [25]. With regard to age, Carbonell *et al*. also observed that T2D patients experiencing lower weight loss at 1 year following LRYGB were typically older compared to their non-T2D counterparts (45 *vs*. 39 years, $p = 0.001$) [20]. Worse metabolic profile is another variable related to postoperative weight loss in T2D patients. In a retrospective cohort study comparing weight loss and metabolic endpoints between patients with and without T2D, matched for age, gender and BMI, Carvalho *et al*. reported that patients with T2D displayed a more unfavourable metabolic profile in baseline, although no difference in weight loss was observed 1 year after LRYGB between groups. However, the T2D patients were the ones who gained most metabolic benefits from the bariatric intervention [21].

An additional variable related to poorer weight loss response following BS is low adherence to nutritional recommendations and physical activity level [25]. Diedisheim *et al*. proposed that alternative strategies should be implemented in patients with T2D after LSG to further improve weight loss response. For example, Mediterranean diet has proven effective in enhancing weight loss outcomes 1 year after both LRYGB and LSG. Engaging in physical exercise after BS is another promising approach to influence post-surgery outcomes and also to prevent weight regain. Finally, the use of liraglutide treatment in bariatric patients with persistent or recurrent T2D may also enhance postoperative weight loss response [4].

With regard to BC, in agreement with previous studies [26], we found out that LSG is able to induce significant decrease in total FM while largely preserving FFM. In our sample, FFM decreased significantly within T2D group at 6 months compared to baseline and remained relatively stable at the second follow-up point. In the non-T2D group, only a slight decrease of FFM occurred within 6 months postoperatively, which was followed by a significant reduction at 12 months post-LSG compared to baseline. FFM was significantly higher at 1 year post-LSG in the T2D group compared to the non-T2D group, but the former also maintained a higher BMI compared to non-T2D individuals. In contrast with our finding, Diedisheim *et al*. reported a significant decrease in FFM at 3 months postoperatively that remained stable until 1 year after LSG in both groups [4]. Preserving FFM is essential in the weight loss process since it is involved in metabolic regulation, functional capacity and skeletal integrity [27]. Loss of muscle tissue is expected to occur predominantly within 6 months following BS. However, the precise amounts of muscle mass lost in specific postoperative phases are difficult to estimate [28]. Since FFM is the most metabolically active tissue in the body a reduction of this compartment may decrease REE, slowing the rate of weight loss after BS. FFM was shown to be positively correlated with resting energy expenditure (REE) after LRYGB, but FM was not. Moreover, a postoperative decline in the REE combined with an increase of caloric intake may

lead to postoperative weight regain. According to recent research, individuals with the lowest level of REE are prone to regain most weight lost after BS [29]. In obesity, low FFM is also associated with the presence of T2D and hypertension [30]. Therefore, preservation of FFM during the postoperative weight loss process following BS is essential. Ideally, weight loss should be limited to the loss of FM%, with total preservation of FFM, but in practice FM% loss is inevitably accompanied by a decrease in FFM as well [31]. Moreover, multiple factors can increase the susceptibility for FFM loss, particularly in the early postoperative phase. An adequate intake of protein is important to prevent FFM loss after BS. A postoperative intake of 1.1 g/kg ideal body weight/day (or 60 g/day) dietary protein is also recommended post-BS to prevent excessive FFM loss. Currently, there are no clinical guidelines defining what amount of FFM loss after BS is excessive. Generally, a FFM loss up to 25% of weight loss is considered acceptable [32]. Muscle protein synthesis is maximized with an intake between 20 - 40 g proteins/meal and resistance exercise. However, bariatric patients are unable to meet these requirements following surgery. Dietary protein intake was shown to decrease at one month postoperatively to approximately 30 g/day due to the overall limitation of food intake (500 - 800 kcal/day), whereas lifting weight is prohibited in bariatric patients up to six weeks post-surgery. In addition, protein restriction in the early postoperative phase leads to muscle tissue breakdown for energetic use [33].

In our sample, patients with T2D lost a significant amount of total FM% compared to baseline at 6 months after LSG, from which point it began to increase. In the non-T2D group, total FM% decreased significantly at both follow-up points as compared to baseline. However, no statistically significant differences between the two groups at 6- and 12- months postoperatively were observed concerning the overall FM% levels. This contrasts with findings of Diedisheim *et al.* which documented a significantly lower total FM loss in patients without T2D compared to patients with T2D at 6- and 12- months postoperatively [4].

WC is considered a surrogate marker for abdominal obesity [7]. Changes in VAT are reflected in WC changes, although the latter does not predict small changes in VAT. WC describes fat distribution, including VAT, which is associated with insulin resistance and major risk for chronic diseases (*e.g.*, cardiovascular diseases, T2D) and mortality [34]. VAT consists of mezenteric and omental fat and its secretion products are drained into the portal circulation, exposing the liver to free fatty acids and cytokines. Subsequent fat accumulation promotes the development of hepatic IR and T2D. Compared to non-T2D individuals, in individuals with T2D VAT is increased and its adipocytes display significant histological alterations, such as cell hypertrophy, stress, degeneration and necrosis. These abnormalities of VAT and ectopic fat accumulation are associated with β-cell dysfunction and T2D [35]. In our sample, at baseline, we did not observe a higher VAT% in patients with T2D compared to patients without T2D. Opposed to our finding, Favre *et al*. showed that patients with T2D submitted to BS exhibited higher VAT% in baseline compared to normoglycaemic patients. Weight loss is related to a decrease in hepatic and pancreatic fat deposition with a subsequent improvement of insulin sensitivity [38]. In our study, patients with T2D did not achieve a significant loss of abdominal fat (expressed as VAT%) at either follow-up point. In contrast, patients without T2D lost a significant amount of VAT% at both 6 and 12 months postoperatively. Diedisheim *et al.* also observed a limited reduction of visceral fat in T2D patients following LSG, proposing that it could exert less favourable effects on cardiometabolic status in the long-term [4].

The worldwide rise of bariatric procedures, including LSG, is not only due to its major effects on weight loss, but also on comorbidities, such as T2D, whose improvement or remission following surgery has been well established. Although they lost less weight and gained less improvement in BC parameters, 58% of our patients with T2D experienced total remission at 1 year after LSG. At the same time, 33% of T2D patients went into partial remission at 6 months post-LSG. Our results are in agreement with those reported by Diedisheim *et al*., respectively a complete T2D remission rate of 52% at 1 year following LSG [4] and also Casajoana *et al*., who observed a 53.3% short-term (1 year) remission rate of T2D after LSG [37].

Certain micronutrients act synergistically to regulate glucose homeostasis and insulin action and their deficiency is believed to contribute to some extent in T2D development [8]. Also, MNDs are common in patients with obesity and bariatric interventions were shown to worsen the micronutrient status of patients [13]. In our sample we did not observe any significant differences pre- and postoperatively within individual groups concerning 25(OH)D, vitamin B_{12}, folate, serum iron and ferritin status. Comparison between the T2D and non-T2D patients also revealed no significant differences between the two groups, except for vitamin B_{12}, whose serum levels were significantly higher among the T2D group. As far as we are aware no study has yet investigated the impact of T2D status on micronutrient status before and after LSG.

The levels of 25(OH)D were deficient (< 10 ng/mL) preoperatively in both groups and remained insufficient (< 20 ng/mL) at 1 year after LSG in all patients, irrespective of T2D status and despite supplementation. There is a large body of evidence indicating that patients with obesity are more likely to have lower plasma 25(OH)D as compared to normal-weight individuals. The prevalence of vitamin D deficiency ranges between 13 - 90% and its insufficiency (defined as 25 (OH)D

levels below 30 ng/mL) is present in up to 98% patients seeking LSG [38]. The precise mechanisms involved are not fully elucidated, but it is assumed that lower sun exposure, low-grade chronic inflammation and volumetric dilution of ingested or endogenously synthesized vitamin D in the fat mass are major contributors [13]. The preoperative vitamin D insufficiency/ deficiency often remains similar after LSG, despite supplementation. Schollenberger *et al*. reported no changes in prevalence of deficiency of serum 25(OH)D levels from baseline (80%) to 12 (72%) and 36 months (76%) post-LSG (n = 39). Patients did not receive postoperative routine supplementation, but if deficient they were advised to take 1000 IU vitamin D (plus calcium) [39].

Interestingly, we found out that vitamin B_{12} levels were significantly higher in the T2D group at both follow-up points as compared to patients without T2D, but keeping within the normal range. Our finding is surprising since vitamin B_{12} deficiency is common among T2D patients, due to either malnutrition or metformin use [11]. Metformin impairs vitamin B_{12} absorption and metabolism in a dose and duration dependent fashion. The reported prevalence of metformin-related vitamin B_{12} deficiency ranges between 5 - 60% among T2D patients. Moreover, the concomitant use of proton pump inhibitors, which is frequent post-LSG, and metformin may increase the risk of vitamin B_{12} deficiency [40]. However, post-LSG metformin use is reconsidered since surgery related improved insulin synthesis and sensitivity leads to rapid amelioration of T2D status or even restoration of euglycaemia [41]. One possible explanation regarding higher levels of circulating vitamin B_{12} in T2D patients comes from Raizada *et al*. which reported that increased duration of T2D was associated with a significant rise of serum of vitamin B_{12} levels [42]. Data concerning the duration of T2D were not available in our study.

Our study has some limitations, particularly regarding its mainly retrospective design that did not include detailed information concerning the duration of T2D. Another limitations of this study are the relative small duration of follow-up period and the relative reduced size of T2D patients sample that could possibly be associated with a certain amount of bias. Also, patients with and without T2D were not matched regarding age.

Conclusions

LSG is a highly effective procedure in lowering body weight and improving BC components. However, compared to their non-T2D counterparts, patients with T2D attained significantly lower %TWL and less improvement in BC at 1 year after LSG. These findings suggest that a better preoperative glycaemic control might induce a better postoperative weight loss response and improved BC profile, but also that LSG is efficient in reducing the cardiometabolic risk factors in T2D patients. 25(OH)D, folate, serum iron and ferritin levels of T2D patients were comparable with those of non-T2D patients. 25(OH)D deficiency/insufficiency persisted postoperatively in all patients, irrespective of T2D status and despite supplementation. Vitamin B_{12} serum concentration was significantly higher at baseline and throughout the study follow-up among the T2D patients *versus* non-T2D patients, but keeping within the normal range. Further research is warranted to corroborate the present study's finding with the effects of T2D on long-term weight status, BC and micronutrient profile following LSG.

Conflict of interest

The authors declare no conflict of interest.

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