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ORIGINAL ARTICLE

Clinical efficacy of bariatric surgery versus liraglutide in patients with type 2 diabetes and severe obesity: a 12-month retrospective evaluation

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Abstract
Aims To evaluate the clinical efficacy of bariatric surgery *vs* medical therapy with liraglutide on weight loss, glycemic control and cardiovascular risk profile in patients with type 2 diabetes and severe obesity.
Methods A retrospective evaluation was conducted in 31 patients with type 2 diabetes and severe obesity who had undergone bariatric surgery and in 31 patients with type 2 diabetes and comparable body weight who had added liraglutide to their background medical treatment in the period 2009–2013. Anthropometric parameters, glycemic control, treatment of diabetes and other comorbidities, safety and side effects before and 12 months after treatment were assessed.
Results Age was 47 ± 8 years (mean ± SD) in bariatric surgery and 56 ± 9 years in medical treatment group ($p < 0.001$); body mass index before treatment was 44 ± 7 and 40 ± 4 kg/m^2 in bariatric surgery and medical treatment, respectively ($p = 0.03$). Twelve months after treatment, average weight loss was 38 ± 15 kg among bariatric surgery patients, and 5 ± 8 kg in medical treatment group ($p < 0.001$). Glycemic control improved in both groups with greater improvement in bariatric surgery patients. The UKPDS risk score decreased in both groups, although it remained higher in medical treatment than in bariatric surgery patients ($p < 0.001$). Of note, almost 60 % of patients on liraglutide met the target of glycated hemoglobin <7 % (53 mmol/mol) and lost ≥5 % of body weight.
Conclusions In severely obese type 2 diabetic patients, bariatric surgery reduced body weight and improved overall metabolic control to a greater extent than medical treatment. Randomized clinical studies are necessary.

Keywords Type 2 diabetes mellitus · Bariatric surgery · Liraglutide · Weight loss

Introduction

Bariatric surgery (BS) has emerged as an effective treatment for morbid obesity based on its efficacy in inducing a stable weight loss and remission of comorbidities in patients with or without type 2 diabetes (T2DM) [1]. BS is recommended in patients with T2DM and a BMI ≥35 kg/m^2 after attempts with lifestyle changes and/or drugs have revealed unsuccessful [2]. The rate of T2DM remission varies from 30 to 95 % according to surgical procedure, with malabsorptive procedures being more effective [1]. BS also results in a considerable improvement of dyslipidemia and arterial hypertension and, more importantly, in a significant reduction in overall and cardiovascular (CV) mortality as well as in cancer incidence [3, 4].

Incretin-based therapy includes a new class of glucose-lowering medications that mimic the effects of glucagon-like peptide (GLP-1), a hormone released from intestinal L cells in response to food intake. Pharmacologic activation of the GLP-1 receptor is known to increase insulin secretion, to inhibit glucagon secretion and hepatic glucose output, and to delay gastric emptying thus improving glycemic control [5]. Several clinical trials have demonstrated that GLP-1 receptors agonists (e.g., exenatide, lixisenatide,

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and liraglutide) added up to metformin and/or other oral agents produce a significant improvement in glucose control without hypoglycemia or weight gain [6]. In addition, in comparative studies with exenatide, liraglutide proved to induce better global diabetes control and potentially favorable effects on CV risk factors [7, 8]. In the light of these characteristics, incretin-based drugs are recommended as add-on therapy in patients not controlled with metformin, according to International guidelines [9]. Currently, no clinical study has compared the clinical efficacy of BS *vs* medical therapy with GLP-1 receptor agonists. The aim of this study was to compare retrospectively the 12-month effect of BS (gastric bypass, GBP or vertical gastrectomy, VG) versus medical therapy with liraglutide on body weight, glucose control, and CV risk profile in patients with T2DM and severe obesity.

Research design and methods

From the database of the Diabetes Center of the Department of Clinical Medicine and Surgery "Federico II" in Naples, we extracted the data of 31 patients with T2DM and severe obesity who had undergone BS and 31 patients, with comparable degree of obesity, who had added liraglutide to their standard hypoglycemic therapy (MTL) because of poor glycemic control in the period 2009–2013. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. All patients gave their informed consent to the use of their clinical and laboratory data and for being included in the study. Data on anthropometric variables, glucose control, lipid profile, arterial blood pressure, drug consumption, and side effects were collected.

In MTL group, liraglutide was added to ongoing hypoglycemic drugs (only metformin in 21 patients; metformin plus sulphonylurea and/or acarbose in the remainders) at the dose of 1.2 mg/die in 20 patients and 1.8 mg/die in the remainders. In the BS group, fifteen patients had undergone RYGB and sixteen SG. All procedures had been performed laparoscopically by the same surgical team according to standard protocols, as previously described [10]. In the surgical group, postoperative management with regard to supplementation of multivitamins and minerals was performed according to International Guidelines [11].

Methods

Plasma concentrations of glucose and lipids were determined by enzymatic assay. LDL cholesterol was calculated with Friedwald formula. HbA1c was evaluated with the HPLC method. All biochemical analyses were performed in a central laboratory.

Statistical analysis

Results were analyzed and expressed as mean ± standard deviation (SD). Differences within each group were evaluated by Student's *t* test for paired data or chi-square, when appropriate. Differences between groups were evaluated by ANOVA, with Scheffè test for multiple comparisons. Comparisons at 12 months were adjusted for age, gender, BMI and duration of diabetes. A p value < 0.05 was considered significant. Therapeutic goals for glucose, blood pressure and lipid control were defined as HbA1c <7 % (53 mmol/mol), systolic blood pressure <140/90 and non-HDL cholesterol <130 mg/dl, respectively. The absolute risk of coronary heart disease was calculated by means of the UKPDS risk engine [12].

Results

Table 1 shows the main clinical and metabolic characteristics of participants at baseline. BS patients were younger (47 ± 8 years) and had a greater mean BMI (44 ± 7 kg/m^2) than MTL patients (age 56 ± 9 years, $p < 0.001$; BMI 40 ± 4 kg/m^2 $p < 0.03$). Duration of diabetes was higher in MTL than in BS patients (9 ± 7 and 4 ± 5 years, $p < 0.001$). Both groups had a poor glycemic control as evidenced by a mean HbA1c ≥7.5 % (58 mmol/mol). BS patients had higher levels of non-HDL cholesterol and triglycerides and lower levels of HDL cholesterol compared to medically treated patients ($p < 0.05$ for all). Both systolic and diastolic blood pressure did not differ between groups at baseline. Hypertension was present in 23 (75 %) and 17 (55 %) of BS and MTL patients, respectively, while the proportion of dyslipidemia was nearly 30–40 % in the two groups (Table 1). The UKPDS risk score was slightly but not significantly higher in the MTL than in the BS group (13.6 ± 8.7 and 8.5 ± 4.5; p = ns).

12-months results

After 12 months (Table 1), surgically treated patients achieved an average weight loss of 38 kg ($p < 0.001$) while MTL patients lost ~5 kg ($p < 0.001$) with 51 % of patients achieving ≥5 % weight loss (Fig. 1). Glycemic control improved in both groups with a HbA1c reduction of −2.2 % (23 mmol/mol) in the BS ($p < 0.001$) and −1.3 % (15 mmol/mol) in the MTL group ($p < 0.001$). In the BS group, non-HDL cholesterol and triglycerides markedly decreased ($p < 0.001$), while HDL cholesterol increased by 30 % ($p < 0.001$) at 12 months. In the MTL group, there

Table 1 Basal characteristics of participants and changes at 12 months

	BS ($n = 31$)			MTL ($n = 31$)			p value between basal	p value between 12 m	p value between Δ
	Basal	12 m	Δ	Basal	12 m	Δ			
Weight (Kg)	122 ± 24	83 ± 14**	−38 ± 14	107 ± 15	102 ± 15**	−5 ± 8	0.004	<0.001	<0.001
BMI (Kg/m^2)	44 ± 7	30 ± 4**	−14 ± 5	40 ± 4	39 ± 5*	−1.4 ± 3	0.03	<0.001	<0.001
FPG (mg/dl)	163 ± 65	79 ± 16**	−84 ± 64	171 ± 56	138 ± 44*	−32 ± 57	ns	<0.001	<0.005
HbA1c (%) (mmol/mol)	7.9 ± 2.1	5.7 ± 0.7**	−2.2 ± 2.1	8.4 ± 1.6	7.0 ± 1.3**	−1.3 ± 1.3	ns	<0.005	ns
	63 ± 21	39 ± 7	23 ± 23	68 ± 16	53 ± 15	15 ± 14			
Total Chol (mg/dl)	211 ± 43	194 ± 50	−17 ± 47	196 ± 32	180 ± 30*	−16 ± 27	ns	ns	ns
HDL Chol(mg/dl)	44 ± 9	58 ± 15**	14 ± 14	51 ± 14	49 ± 11	−1.6 ± 10	<0.05	<0.001	<0.001
Non-HDL Chol. (mg/dl)	166 ± 42	135 ± 47**	−31 ± 43	145 ± 27	131 ± 27*	−14 ± 28	<0.05	ns	ns
Triglyceride(mg/dl)	190 ± 79	99 ± 54**	−91 ± 69	145 ± 38	152 ± 64	6.4 ± 59	<0.05	<0.005	<0.001
SBP (mmHg)	128 ± 13	128 ± 17	0 ± 18	134 ± 20	128 ± 9	−6 ± 21	ns	ns	ns
DBP (mmHg)	76 ± 6	76 ± 9	0 ± 13	84 ± 12	81 ± 5	−3 ± 14	ns	ns	ns
UKPDS risk score	8.5 ± 4.5	3.9 ± 2.4**	−4.6 ± 3.7	13.6 ± 8.7	8.9 ± 5.2	−4.7 ± 5.8	ns	<0.001	ns

Comparisons at 12 months were adjusted for age, gender, BMI and duration of diabetes

BS bariatric surgery, *MTL* medical treatment with liraglutide, *BMI* body mass index, *FPG* fasting plasma glucose, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *UKPDS* United Kingdom Prospective Diabetes Study; Δ absolute changes (12 months minus basal)

* $p < 0.05$, ** $p < 0.001$ basal versus 12 months within each group

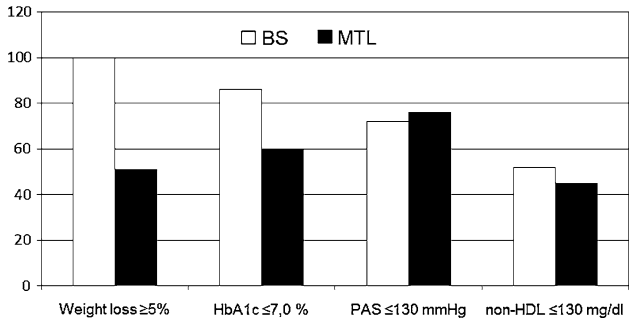

Fig. 1 Proportion of patients reaching the therapeutic targets in the BS and MTL groups

was a significant reduction in total and non-HDL cholesterol, while triglycerides and HDL cholesterol remained unchanged. The UKPDS risk score decreased significantly in both the BS and MTL groups, although it remained higher in MTL compared with BS patients (3.9 ± 2.4 vs 8.9 ± 5.2; $p < 0.001$).

Figure 1 illustrates the proportion of patients meeting the therapeutic goals for glucose, blood pressure and lipid control at 12 months. HbA1c <7 % (53 mmol/mol) was reached in 86 and 60 % of BS and MTL patients, respectively ($p < 0.03$). The proportion of patients reaching blood pressure and lipid goals did not differ between the two groups. However, the large majority of surgically treated patients discontinued medications, whereas none of the TML group withdrew pharmacologic therapy for diabetes and comorbidities (Table 2).

Side effects

The number of side effects registered over 12 months was higher in BS than in MTL patients (34 vs 7). Among surgically treated patients, one patient developed acute renal failure 1 week after surgery due to severe dehydration, which went to complete resolution in 1 week. Another frequent adverse event was symptomatic reactive hypoglycemia that was diagnosed in eight patients (five in the RYGB group and three in the SG group) by means of continuous glucose monitoring. This condition was successfully controlled with low-glycemic index diet associated, in two patients, with pre-meal acarbose. Other manifestations were hypoferritinemia (7 pts), anemia (3 pts), electrolytic imbalance (8 pts), and vitamin deficit (6 pts). Among medically treated patients, the main side effect was nausea but not so severe to lead to liraglutide discontinuation. One patient complained frequent episodes of vomit associated with abdominal pain that spontaneously disappeared after 1 month.

Table 2 Use of medications from baseline to 12 months

	BS ($n = 31$)		MTL ($n = 31$)	
	Basal	12 months	Basal	12 months
Only diet	4 (13 %)	28 (90 %)	0	0
1 Medication for T2DM	22 (71 %)	3 (10 %)	21 (68 %)	20 (64 %)
2 Medications for T2DM	5 (16 %)	0	7 (22 %)	8 (26 %)
≥3 Medications for T2DM	0	0	3 (10 %)	3 (10 %)
Hypertension,	23 (74 %)	2 (6 %)	17 (55 %)	19 (61 %)
Dyslipidemia	10 (32 %)	2 (6 %)	13 (42 %)	14 (45 %)

Data are expressed as number (n) and percentage (%)

BS bariatric surgery, *MTL* medical treatment with liraglutide

Discussion

In this retrospective study, we assessed the clinical effects of bariatric procedures (GBP and VG) compared with medical treatment with liraglutide in patients with T2DM and high degree of obesity. Our data show that BS is more effective in reducing body weight and CV risk profile than MTL; in fact, more than 87 % of surgically treated patients achieved a good result at 12 months defined, according to MacLean classification [13], as a BMI <35 kg/m^2. In addition, BS provided better glucose control with little or no need for glucose-lowering agents compared with medical therapy. Actually, 85 and 60 % of BS and MTL patients, respectively, achieved the goal of HbA1c ≤7 % (53 mmol/mol), a finding of great clinical relevance for the reduction/prevention of CV complications [14].

Our data are in agreement with recent studies comparing the clinical outcome of different surgical procedures with medical therapy in patients with T2DM and high degree of obesity [15–18]. These studies, together with recent meta-analyses examining clinical trials with a follow-up of at least 6 months [19, 20], demonstrated the advantage of the surgical approach over medical therapy in terms of weight loss, remission of T2DM and associated comorbid conditions, and reduction of medications usage [19, 20]. However, in these studies, medical therapy included standard oral hypoglycemic agents and/or insulin with very few patients treated with incretin-based therapy. Using a retrospective approach, our study is the first to compare bariatric surgery *vs* GLP-1 receptor agonists, which is considered the optimal add-on therapy in patients with T2DM and obesity inadequately controlled with metformin. Although the superiority of bariatric surgery in reducing body weight and improving overall metabolic control is inescapable, the beneficial effects of liraglutide as add-on therapy deserve consideration. Actually, more than half the patients treated with liraglutide achieved weight loss ≥5 and 60 % of them reached the HbA1c target ≤7 % (53 mmol/mol) at 12 months. This finding is of clinical relevance in the light of previous studies demonstrating that loss >5, <10 % of initial weight is sufficient to produce a clinically significant improvement in CV risk factors in individuals with T2DM and severe obesity [21]. In line with these observations, we found a significant reduction in CV risk score in our patients treated with liraglutide; such reduction could result from weight loss together with a possible direct cardioprotective effect of liraglutide [22]. Ongoing studies will provide conclusive data on the cardiovascular safety of liraglutide [23]. Noteworthy is that MTL patients were older and had a longer duration of diabetes and a worse glycemic control than surgical patients; thus, it could be expected that adding liraglutide earlier in the course of the disease may produce an even better clinical response.

In surgically treated patients, there was an overall improvement of cardiovascular risk profile, further emphasized by the discontinuation/reduction of the use of hypolipidemic and antihypertensive drugs. We found a significant reduction in both non-HDL cholesterol and triglycerides and a 30 % increase in HDL cholesterol, confirming the notion that BS dramatically improves lipid metabolism through multiple mechanisms, including reduced lipid absorption [10]. Noteworthy is that also MTL patients improved lipid profile with a significant reduction in total and non-HDL cholesterol levels; it is conceivable that better outcomes could be obtained combining liraglutide with lifestyle intensive intervention [24].

An important complication registered in the BS group was reactive hypoglycemia that occurred in nearly 25 % of our patients; the unexpectedly high frequency compared with that reported in the literature probably depends on the use of continuous glucose monitoring system, which detects low glucose levels even in asymptomatic patients. This complication is likely a consequence of the rapid nutrient delivery in the intestine, which leads to GLP-1–mediated insulin hypersecretion [25]. Some authors provocatively interpreted this condition as an "extreme" form of improvement in systemic metabolism induced by bariatric surgery [26].

The limitations of this study include its retrospective design, the limited sample size, and the single-center experience. The strength is that all clinical and biochemical

measurements were performed centrally; this standardization reduces any possible inaccuracy in the comparison between the two groups.

In summary, bariatric surgery is more effective than medical therapy with liraglutide to achieve weight loss and glucose control in patients with T2DM and severe obesity. Noteworthy, liraglutide as add-on therapy is able to produce a clinically relevant weight loss and an optimal glucose control in more than half of patients. This finding underscores the need to implement intensive lifestyle intervention in association with incretin-based therapy as one possible strategy to treat patients with T2DM and high degree of obesity who have limited access to, or refuse the surgical approach. Since obesity and T2DM are chronic disorders, the efficacy, and safety of these interventions and also the durability of benefits have to be confirmed in long-lasting clinical trials.

Conflict of interest Mariella Cotugno, G. Nosso, G. Saldalamacchia, G. Vitagliano, E. Griffo, R. Lupoli, L Angrisani, G. Riccardi, B. Capaldo declare that they have no conflict of interest.

Ethical standards All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008.

Informed consent Informed consent was obtained from all patients for being included in the study.

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