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SHORT COMMUNICATION

Changes induced by metabolic surgery on the main components of glucose/insulin system in patients with diabetes and obesity

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Introduction

Bariatric surgery is able to induce remission of type 2 diabetes (T2D). Several studies reported an improvement of insulin sensitivity after surgery [1], but data about insulin secretion and insulin clearance are less abundant and somewhat controversial [2, 3]. Aim of our study was to assess the changes of the determinants of glucose regulation, i.e., insulin secretion, insulin sensitivity and insulin clearance in a group of T2D patients with obesity one month and over 1 year after metabolic surgery.

Methods

Ten (M/F = 5/5) patients with T2D and obesity (mean ± SD: duration of diabetes: 5.6 ± 1.3 years, BMI: 45.2 ± 1.8 Kg/m^2) candidate for sleeve gastrectomy (SG) or gastric bypass (RYGB) were recruited for the protocol approved by the Local Ethical Committee (CE 2170) and registered as NCT01767441. Remission of diabetes was defined according to HbA1c value < 42 mmol/mol Hb and FBG < 5.6 mmol/l off diabetic medications for at least 12 months. A 5 h-mixed meal test (MMT: containing 186 kcal obtained from 30 g of corn flour as carbohydrates and from 20 g of parmesan-cheese as protein and fat) was performed before (MMT0), 1 (MMT1) and 12 months (MMT12) after surgery. Fasting plasma glucose (FPG), Insulin, C-peptide, glucagon, glucagon-like peptide1 (GLP-1) and gastric inhibitory polypeptide (GIP) were measured at the times as reported in Fig. 1. Beta-cell function (BCF) and insulin-clearance were assessed by mathematical modeling as, previously reported [4]. β-cell function is described by two components: one related to the rate of increase in plasma glucose (DC: derivative control) and the other related to glucose concentration per se (PC: proportional control). As β-cell function and insulin clearance influence insulin bioavailability and the latter is derived from PC, we calculated insulin bioavailability as adjusted PC (PCadj) according to the formula: PCadj = σ2/insulin clearance [5]. PCadj (pmol/mmol) provides an index of the increase in insulin bioavailability (pmol/L) in response to an increase in glucose concentration of 1 mmol/L. To better understand the changes of insulin bioavailability in response to glucose and IS over time, we plotted the trajectory of the changes of PCadj and OGIS over time [5]. A rightward and/or upward trajectory hallmarks the improvements in glucose regulation, whereas a leftward and/or downward trajectory indicates a worsening in glucose regulation. All comparisons were carried out by nonparametric tests (Friedman test and subsequent Wilcoxon test when appropriate). Statistical significance was set at $p < 0.05$. Insulin sensitivity (IS) was estimated with the oral glucose insulin sensitivity index (OGIS).

Riccardo C. Bonadonna and Enzo Bonora jointly supervised this study.

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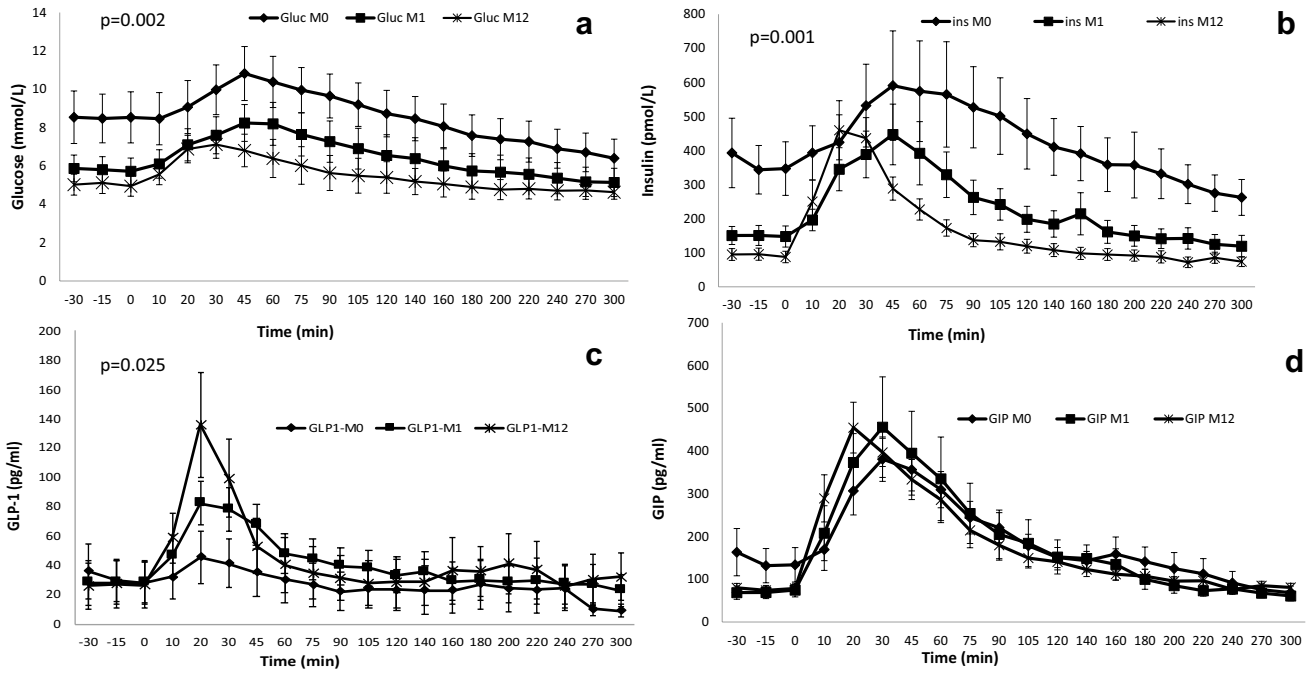

Fig. 1 Plasma levels of glucose (**a**), insulin (**b**), GLP-1 (**c**), GIP (**d**) curves during MMT at baseline (M0), 1 month (M1) and 12 months (M12) after bariatric surgery. P values calculated by Friedman test. Each dot in the curves is Mean ± Standard error of the mean

Results

Three subjects underwent SG and seven subjects underwent RYGB. After surgery, body weight consistently decreased at 1 month (Δweight: − 13.5 kg) and at 1 year (Δweight: − 36.2 kg). Eight patients showed diabetes remission at 12 months.

During MMT after surgery:

1 FPG and the area under the glucose concentration curve ($AUC_{glucose}$) in response to MMT, significantly decreased at 1 and 12 months after surgery.
2 Fasting plasma insulin concentrations showed marked reductions at 1 and 12 months after surgery. $AUC_{insulin}$ was reduced by 40% and 56% at MMT1 and MMT12, respectively.
3 Fasting GLP-1 concentration did not change both a 1 month and 12 months, whereas the AUC of GLP-1 during the MMT progressively increased over the time, showing a progressively higher early peak after surgery.
4 Fasting GIP significantly decreased 1 month after surgery and remained stable at 1 year. No significant changes in AUC of GIP during the MMT were observed after surgery (Fig. 1).
5 No significant changes in glucagon fasting levels and in the AUC of glucagon after surgery were detected (data not shown).
6 A nonsignificant trend of improvement in both DC and PC ($p = 0.236$ and $p = 0.097$, respectively) (Fig. 2) and no significant changes in insulin clearance were observed ($p = 0.407$). A graded, significant improvement of IS was observed at 1- and 12-month ($p = 0.001$).
7 The changes over the time of insulin bioavailability in response to the meal (PCadj) and IS (OGIS-2 h) showed an evident rightward trajectory as in Fig. 2, which could explain the improvement in glucose regulation as depicted in Fig. 1.

Discussion

This study evaluated the short (1 month) and sustained (12 months) effects of metabolic surgery on the main determinants of glucose regulation and the incretin response to MMT in 10 patients with T2D and obesity. Metabolic surgery induced a significant weight loss, an improvement in glucose homeostasis and a remission of diabetes in 80% of patients. The improvement in glucose homeostasis could be put in motion by the combination of caloric restriction and by changes in gut hormone secretion. The improvement in the GLP-1 curve during MMT could have had positive effect on β-cell function, even if the changes of DC and PC, observed at both 1 and 12 months after surgery, did not reach statistical significance. In contrast, IS increased by about 65%, consistent with results from previous studies [1]. To

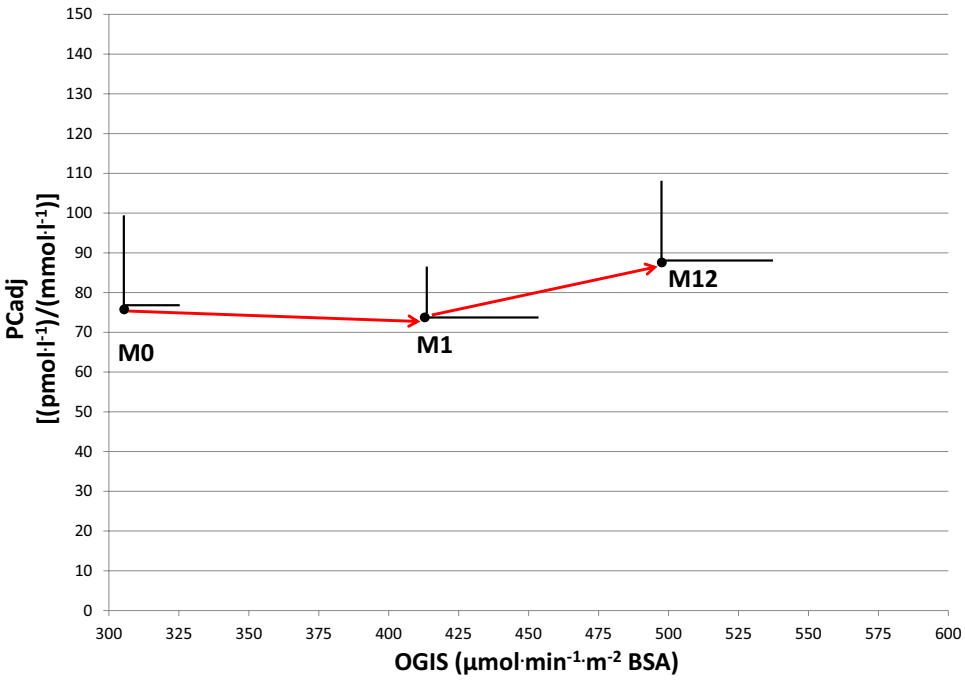

Fig. 2 Joint changes in insulin bioavailability in response to glucose (PCadj; y axis) and insulin sensitivity (OGIS; x axis) during 12 months of follow-up. In this vector plot, a rightward and/or upward trajectory hallmarks the improvements in glucose regulation, whereas a leftward and/or downward trajectory indicates a worsening in glucose regulation. Data are Mean ± Standard error of the mean

better explain the physiological changes observed after bariatric surgery in our subjects, we explored the dynamic interplay between BCF, insulin clearance and IS. BCF and insulin clearance affect insulin bioavailability (PC_{adj}) which forms a physiological feedback loop with IS to regulate glucose homeostasis [4]. The vector plot showed a rightward trajectory, which is explanatory for the sustained improvement in glucose regulation and for diabetes remission in 8 out of 10 patients after metabolic surgery. However, a longer follow-up is needed to monitor further changes in insulin bioavailability. The main strength of our study is the simultaneous assessment of BCF, insulin clearance and IS to explore the joint changes in all these metabolic parameters one month and over 1 year during real world mixed meal test after the metabolic surgery. The main limitation is the low number of subjects enrolled: it made it difficult to detect the effect of each surgical procedure on the determinants of glucose regulation and also to observe potentially significant changes in BCF and insulin clearance. In conclusion, metabolic surgery in subjects with T2D and obesity yields an amelioration of glucose homeostasis due to a marked improvement in IS, detectable already soon after surgery.

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Author contributions RCB and MGZ were involved in conception and design. RCB and EB were involved in critical revision and study supervision. ER, MGZ and MT drafted the manuscript. MLB and LS performed statistical analysis. MLB and RCB were involved in mathematical modeling. ER, MT, MLB, LS, RCB and EB analyzed and interpreted the data. ER, GC, AA and MB were involved in data acquisition.

Compliance with ethical standards

Conflict of interest No potential conflicts of interest relevant to this article were reported.

Ethical standard statement The study has been reviewed by the ethics committee and have therefore been performed in accordance with the ethical standards laid down in an appropriate version of the 1964 Declaration of Helsinki.

Informed consent All subjects gave their informed consent prior to their inclusion in the study.

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