

Acarbose Improves Hypoglycaemia Following Gastric Bypass Surgery Without Increasing Glucagon-Like Peptide 1 Levels

Juan Patricio Valderas · Jessica Ahuad · Lorena Rubio · Manuel Escalona · Felipe Pollak · Alberto Maiz

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Abstract

Background Postprandial hypoglycaemia is a severe complication of Roux-en-Y gastric bypass (RYGBP). Acarbose, an α -glucosidase inhibitor (AGI), is employed in its treatment. Several studies have shown that AGIs increase the postprandial levels of glucagon-like peptide 1 (GLP-1). However, an excessive level of GLP-1 is one of the factors involved in the physiopathology of this condition. We analysed the effect of acarbose oral administration in eight RYGBP patients with clinically significant hypoglycaemia or dumping syndrome.

Methods Glucose, insulin and GLP-1 plasma levels in fasting and after ingestion of a standard meal (Ensure Plus®; 13 g protein, 50 g carbohydrate, 11 g fat) were measured. The test was repeated the following week with the oral administration of 100 mg of acarbose 15 min prior to the meal.

Results Five patients developed asymptomatic hypoglycaemia during the test (glucose level <50 mg/dl) with inappropriately high insulin levels and exaggerated GLP-1 response. Acarbose ingestion avoided hypoglycaemia in all of the patients and increased the lowest plasma glucose level (46.4 ± 4.8 vs. 59.0 ± 2.6 mg/dl, $p < 0.01$). Acarbose ingestion decreased the area under the curve for serum insulin and GLP-1 levels at 15 min after the meal.

Conclusions Acarbose avoided postprandial hypoglycaemia following RYGBP by decreasing the hyperinsulinemic response. This was associated with a decrease in early GLP-1 secretion, in contrast to that observed in non-surgical subjects. This finding could be explained by the reduction of

glucose load in the jejunum produced by the α -glucosidase inhibition, which is the main stimulus for GLP-1 secretion.

Keywords Glucagon-like peptide 1 · Acarbose · Hypoglycaemia · Gastric bypass

Introduction

The prevalence of postprandial neuroglycopenia, a severe complication of Roux-en-Y gastric bypass surgery (RYGBP), is not known. According to a recent publication, patients with a RYGBP have a twofold to sevenfold relative risk of developing severe hypoglycaemia and other related conditions [1]. An increasing number of patients unresponsive to medical treatment have required partial or total pancreatectomy to avoid the life-threatening complication of neuroglycopenia [2, 3].

Acarbose, an α -glucosidase inhibitor (AGI), is empirically employed in the medical management of post-RYGBP hypoglycaemia [4]. This drug, along with miglitol and voglibose, is a competitive inhibitor of pancreatic α -amylase and intestinal brush border α -glucosidases producing a delayed hydrolysis of ingested polysaccharides, oligosaccharides and disaccharides to monosaccharide. Consequently, the postprandial rise in plasma glucose is blunted and prolonged, which decreases insulin secretion [5]. Several studies have shown that the AGIs increase the postprandial levels of glucagon-like peptide 1 (GLP-1) in normal and diabetic subjects. This is most likely due to a reduction in carbohydrate absorption in the proximal part of the small bowel, which increases the load of these nutrients in the distal intestine where the secretion of GLP-1 is greater [6–8]. This is important because the increase of the GLP-1 is one of the mechanisms involved in the physiopathology of hyperinsulinemic hypoglycaemia [2, 3, 9, 10].

J. P. Valderas (✉) · J. Ahuad · L. Rubio · M. Escalona · F. Pollak · A. Maiz

Department of Nutrition, Diabetes and Metabolism,
School of Medicine, Pontificia Universidad Católica de Chile,
Santiago, Chile
e-mail: jpvalder@uc.cl

We reported the plasma levels of glucose, insulin and GLP-1 during a meal tolerance test (MTT) in eight patients with clinically significant hypoglycaemia or late dumping syndrome after RYGBP with or without the previous oral administration of acarbose.

Methods

The Ethics Committee of the Pontificia Universidad Catolica de Chile School of Medicine approved this study. Eight symptomatic patients who were under control in the Obesity Surgical Treatment Program were recruited. Neuroglycopenic symptoms of postprandial hypoglycaemia included fatigue, confusion and loss of consciousness. For the MTT, subjects were dated at 8 AM, after a 12-h overnight fast. While in a sitting position, a venous catheter was placed in the forearm of each patient. Blood samples were drawn before and at 15, 30, 45, 60, 90, 120 and 180 min after the intake of 237 ml of a standard liquid meal (STM; Ensure Plus®—355 kcal, 13 g protein, 50 g carbohydrate, 11 g fat; Abbott Laboratories, Columbus, OH, USA). We decided to use this STM because it contains maltodextrin and other polysaccharides which are substrates for α -glucosidase enzyme in the gut, and this meal reproduces the nutrient composition of a common breakfast recommended for these patients. The test was repeated the following week with the oral administration of 100 mg of acarbose (Glucobay®, Bayer HealthCare Laboratories, Germany) 15 min prior to the meal.

Assays

Blood samples were placed in tubes containing EDTA and a protease inhibitor (Trasyol, 500 kIU/ml; Bayer, Leverkusen, Germany), immediately centrifuged at 4°C during the collection period and stored at -70°C until analysed. Glucose levels were measured by the glucose oxidase method (Human, Wiesbaden,

Germany). Insulin levels were measured by radioimmunoassay (Siemens Healthcare Diagnostics, Deerfield, IL, USA). Plasma GLP-1 concentrations were measured by an in-house sandwich-type ELISA (HYB 147-06, AntibodyShopR, Denmark). The assay, described previously [11], had an intra-assay variation coefficient of <10% and an inter-assay variation coefficient <10%, and it detects all forms of GLP-1 truncated at the N-terminus (36).

Statistical Analysis

Data are expressed as the mean \pm standard error of the mean (SEM). The Kolmogorov–Smirnov test was used to assess the normality of distribution. Values for the area under the curve (AUC) for glucose, insulin and total GLP-1 levels after the STM were calculated using the trapezoidal method and were compared with non-parametric test (Wilcoxon test) due to the small sample size. A repeated measure ANOVA, followed by a Bonferroni post hoc test, was used to analyse the effect of the treatments and time points. Statistical analysis was performed using GraphPad Prism (GraphPad Software, Inc., La Jolla, CA, USA). A *p* value <0.05 was considered significant.

Results

We recruited patients with a RYGBP who consulted for neuroglycopenic symptoms that suggested postprandial hypoglycaemia. We studied the first eight patients willing to participate. The patients were 43.4 \pm 3.4 years old, the presurgery BMI was 39.1 \pm 1.32 kg/m² and the current BMI was 25.3 \pm 4.8 kg/m². Four of the patients had type 2 diabetes before RYGBP and all of them achieved a complete remission after the surgery. The clinical presentation of the hypoglycaemic or dumping syndrome events is described in Table 1. Five patients had a documented hypoglycaemia by capillary or

Table 1 Clinical presentation of hypoglycaemia after RYGBP and values observed during MTT with or without acarbose

Subject	Onset symptoms since RYGB (months)	Clinical description	Postprandial timing (min)	Glucose level (mg/dl) during episode	Lowest glucose level (mg/dl) during MTT	Lowest glucose level (mg/dl) during MTT with acarbose
A	7	Motor vehicle accident	120	42	26 (90 min)	55 (60 min)
B	16	Confusion, fatigue	45	Not assessed	53 (90 min)	71 (45 min)
C	17	Confusion, fatigue	90	36	47 (90 min)	51 (90 min)
D	36	Confusion, fatigue	45	45	40 (60 min)	55(60 min)
E	12	Loss of consciousness	Not reported	Low	35 (90 min)	53 (60 min)
F	9	Loss of consciousness	120	23	43 (60 min)	56(60 min)
G	40	Confusion, fatigue	90	Not assessed	59 (60 min)	69 (90 min)
H	2	Confusion, fatigue	45	Not assessed	68 (60 min)	62 (60 min)

RYGBP Roux-en-Y gastric bypass, MTT meal tolerance test

plasma glucose measure lower than 50 mg/dl. The other three patients could not measure their glucose levels during the

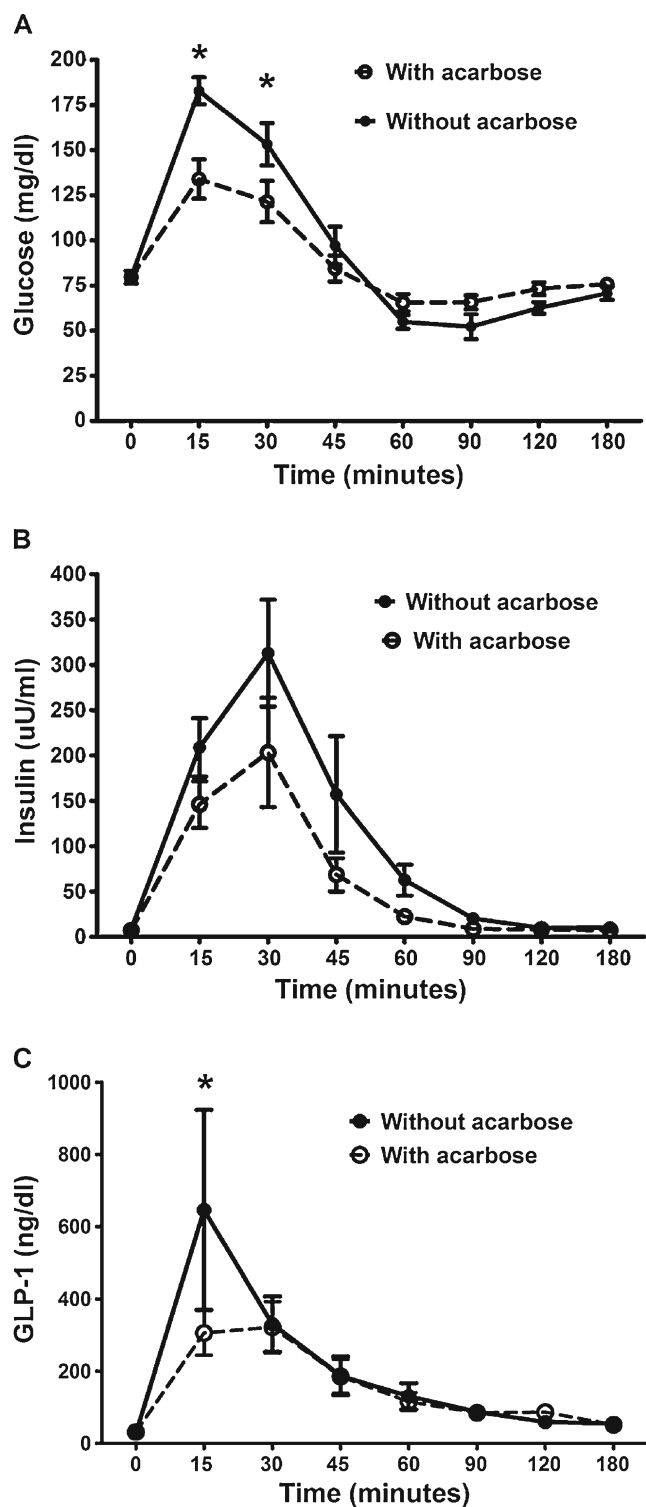


Fig. 1 Plasma levels of glucose (a), insulin (b) and total GLP-1 (c) with and without acarbose in response to the standard liquid meal. * p value <0.05 for comparisons at different time points without and with acarbose (ANOVA for repeated measures followed by Bonferroni post hoc analysis)

symptomatic episode. Plasma glucose levels during the MTT are shown in Fig. 1a. The five subjects with previous documented hypoglycaemia had glucose levels lower than 50 mg/dl during the MTT associated with mild symptoms. The acarbose ingestion was associated with a significant increase in the lowest glucose plasma levels, while none of the patients had a glycaemia lower than 50 mg/dl (Table 2). A significant diminution was observed in the difference between the peak and nadir levels of plasma glucose of patients without and with acarbose (136.5 ± 5.3 vs. 76.1 ± 10.8 mg/dl, respectively, $p=0.0003$). There was no change in the AUC for plasma glucose (Table 2). An exaggerated insulin and GLP-1 plasma level response to the meal was observed (Fig. 1b, c). We observed significant reductions in several indices for insulin secretion obtained from the MTT following the acarbose ingestion: the AUC for plasma insulin, the AUC insulin to the AUC glucose ratio and the increase of 0 to 30 in insulin levels (Table 2). The oral administration of acarbose was associated with a significant decrease in the GLP-1 levels 15 min after the ingestion of the liquid meal (Fig. 1c) without changes in the other time points.

Discussion

We are the first researchers to analyse the acute effects of acarbose on glucose, insulin and GLP-1 plasma levels in subjects with hypoglycaemia following RYGBP. As observed in non-surgical subjects, the oral administration of acarbose reduced the postprandial hyperglycaemia, prevented the reactive hypoglycaemia and blunted the insulin hypersecretion. On the other hand, and in contrast to non-surgical subjects [6–8], the oral administration of acarbose before a meal did not produce an increase in postprandial levels of GLP-1. Additionally, a reduction in postprandial levels was observed at 15 min. This finding is important, because the robust

Table 2 Glucose and insulin plasma levels during the meal tolerance test without and with acarbose

	Without acarbose (n=8)	With acarbose (n=8)	p value
Plasma glucose lowest level (mg/dl)	46.4 ± 4.8	59.0 ± 2.6	0.03
Maximum to minimum plasma glucose ratio	4.18 ± 0.4	2.33 ± 0.2	0.001
AUC for insulin (μ U/ml/min)	$12,998 \pm 2,337$	$7,659 \pm 1,629$	0.008
AUC_{ins} / AUC_{glu}	0.90 ± 0.18	0.52 ± 0.11	0.008
$\Delta Insulin_{30}$ (μ U/ml)	304.1 ± 58.6	196.0 ± 59.3	0.02

Values are mean \pm SEM

AUC area under the curve, $\Delta Insulin_{30}$ increase of insulin levels from 0 to 30 min

secretion of GLP-1 in response to meals has been a factor involved in the pathogenesis of this condition due to the insulinotropic and trophic effect of this entero-peptide on pancreatic beta cell [2, 10]. Although the hypoglycaemic effect of GLP-1 is glucose dependent, Toft-Nielsen et al. have shown that the exaggerated GLP-1 response to nutrients in patients with accelerated gastric emptying could be responsible for their high incidence of postprandial reactive hypoglycaemia. Through intravenous infusions, they induced hypoglycaemia in normal volunteers reproducing the glucose and GLP-1 plasma level profile observed in gastrectomised patients [12]. Supporting that observation, Goldfine et al. described higher GLP-1 fasting and postprandial levels in patients with RYGBP and neuroglucopenic hypoglycaemia compared with RYGBP asymptomatic subjects [10]. The effect of acarbose on GLP-1 levels in our patients with a RYGBP was unexpected. Similar findings after acarbose administration on GLP-1 levels were reported by Imhof et al. in one patient with oesophagectomy with cervical anastomosis [13]. The exact mechanisms whereby nutrients induce the GLP-1 secretion by L cells are unclear. Although fat and protein ingestion resulted to an increase in GLP-1 secretion, carbohydrates are the main stimulus. Some studies suggest that the glucose absorption by L cells is necessary for the release of GLP-1 observed after carbohydrate intake [14]. It is likely that the α -glucosidase inhibition slows the digestion of the carbohydrates contained in STM and strongly reduces the glucose absorption in subjects with RYGBP. However, changes in other variables after RYGBP, like weight loss or glycaemic status, may also explain these findings.

The absence of an increase in GLP-1 levels after the acarbose oral administration has other important effects. Acarbose is widely prescribed off-label for the treatment of postprandial hypoglycaemia in patients with RYGBP. The trophic effects of GLP-1 on the beta and duct cells of the pancreas, clearly proven in animal studies [15], could induce the development of nesidioblastosis and insulinoma in these patients. However, the existence of nesidioblastosis following RYGBP in human subjects is a matter of controversy between researchers [16–18]. Even more, severely obese patients could have a beta cell defect that promotes hyperinsulinism and islet cell hyperplasia previous to the RYGBP. If this phenomenon is real, our findings suggest that the administration of acarbose in the treatment of these patients would not induce an additional increase of the GLP-1 effect on beta cell mass.

MTT was not employed in this study in the diagnosis of postprandial hypoglycaemia. A high percentage of asymptomatic subjects have low glucose levels after an oral load. Also, hyperinsulinemic obese patients could develop hypoglycaemic symptoms before surgery, and after weight reduction, these symptoms disappear. Therefore, the diagnosis and the need of treatment and further evaluations must be

determined for the severity of manifestations during free living. The use of continuous glucose monitoring in this type of patients may be helpful for the diagnosis [19].

In this study, we use a plasma glucose value less than 50 mg/dl to define hypoglycaemia, although we are aware that it is controversial. We employed the value defined in the Third International Symposium on Hypoglycemia for postprandial hypoglycemia [20]. Recently, the Endocrine Society Statement Clinical Practice Guideline defined a glycaemia value less than 55 mg/dl [21]. Six patients were under this value during the MTT and two persisted with plasma glucose value less than 55 mg/dl during the MTT after acarbose ingestion. A high proportion of our volunteers had T2D before the surgery. Postprandial hypoglycaemia is seen but less frequently in diabetic patients. In these subjects, drug-induced hypoglycaemia is common; therefore, they are educated to recognise and report this event.

The lack of glucose absorption measurements is the main weakness of this study. A greater sample size and long-term studies are necessary to strongly establish the effect of the acarbose administration on GLP-1 levels in patients with hypoglycaemia following RYGBP and the clinical evolution of the patients.

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Conflicts of Interest Juan Patricio Valderas, Jessica Ahuad, Lorena Rubio, Manuel Escalona, Felipe Pollak, and Alberto Maiz have no conflicts of interest to declare.

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