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RESEARCH ARTICLE

GLP-1 and Adiponectin: Effect of Weight Loss After Dietary Restriction and Gastric Bypass in Morbidly Obese Patients with Normal and Abnormal Glucose Metabolism

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Abstract
Background It has been proposed that there is improvement in glucose and insulin metabolism after weight loss in patients who underwent diet restriction and bariatric surgery.
Methods Eleven normal glucose tolerant (NGT) morbidly obese patients [body mass index (BMI), 46.1±2.27 g/m^2] and eight abnormal glucose metabolism (AGM) obese patients (BMI, 51.20 kg/m^2) were submitted to diet-restriction and bariatric surgery. Prospective study on weight loss changes, over the glucose, insulin metabolism, glucagon-like peptide-1 (GLP-1), and adiponectin levels were evaluated by oral glucose tolerance test during three periods: T1 (first evaluation), T2 (pre-surgery), and T3 (9 months after surgery).
Results Insulin levels improved after surgery. T1 was 131.1± 17.60 pmol/l in the NGT group and 197.57±57.94 pmol/l in the AGM group, and T3 was 72.48±3.67 pmol/l in the NGT group and 61.2±9.33 pmol/l in the AGM group. The major reduction was at the first hour of the glucose load as well as fasting levels. At 9 months after surgery (T3), GLP-1 levels at 30 and 60 min had significantly increased in both groups. It was observed that the AGM group had higher levels of GLP-1 at 30 min (34.06±6.18 pmol/l) when compared to the NGT group (22.69±4.04 pmol/l). Homeostasis model assessment of insulin resistance from the NGT and AGM groups had a significant reduction at periods T3 in relation to T1 and T2. Adiponectin levels had increased concentration in both groups before and after surgical weight loss. However, it did not have any statistical difference between periods T1 vs. T2.
Conclusions Weight loss by surgery leads to improvement in the metabolism of carbohydrates in relation to sensitivity to the insulin, contributing to the reduction of type 2 diabetes incidence. This improvement also was expressed by the improvement of the levels of adiponectin and GLP-1.

Keywords GLP-1 · Adiponectin · Morbid obesity · Gastric bypass surgery · Glucose metabolism disorders · Insulin resistance

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Introduction

Obesity is characterized as a metabolic disease by having insulin resistance and hyperinsulinemia [1], and it is the most important risk for developing type 2 diabetes mellitus. In the beginning, it was thought that the skeletal muscle

was the main place for the insulin resistance [2], but today, the adipose tissue has been identified as the major site for this resistance [3].

Insulin resistance and type 2 diabetes are closely related to body mass index (BMI), a marker of overall obesity [4]. The risk of developing diabetes becomes higher with the increase of the BMI: 58 times higher in women with BMI> 35 kg/m^2 than in women with BMI of 22 kg/m [2, 5].

An increasing number of obese patients are looking for a bariatric operation to lose weight, and >30% of the patients who underwent this procedure have type 2 diabetes [6, 7]; the surgery results in a loss of 50% to 70% of weight, and the "cure" in 77% of the diabetes [8].

It is proposed that the metabolic improvement occurs because of some incretins, and the incretins could be some of the key mediators of the antidiabetic effect of certain types of bariatric surgeries [9]. One of these is glucagon-like peptide-1 (GLP-1) (7–36) amide. It was demonstrated that GLP-1 inhibits gastric emptying, gastric acid secretion, and glucagon secretion. In the central nervous system, GLP-1 induces satiety, leading to reduced weight gain. In the pancreas, GLP-1 is now known to induce expansion of the insulin-secreting beta-cell mass and enhance insulin secretion [10]. It has also been proposed that it functions as an enterogastrone factor [11]. GLP-1, its proven insulinotropic properties per se [12, 13], antidiabetic character [11], and stimulatory action upon both the expression of glucotransporter genes [14], and the transport and metabolism of glucose outside of pancreatic tissue [13, 15, 16] exert a dual effect in normal rats and human adipocytes, stimulating not only the mechanism of lipogenesis but also that of lipolysis [16–19].

The action of this peptide on the beta cell seemed to be preserved in patients with type 2 diabetes, with the intravenous infusion of 1 pmol kg^{-1}. Min-1 of GLP-1 has a fast effect in normalizing the hyperglycemia [20]. Several studies have shown that the significant loss of weight by bariatric surgery was followed by the control of diabetes and increasing levels of GLP-1 [21].

Besides incretins, other hormones increase after weight loss and are related to glucose metabolism. A hormone secreted by the adipose tissue is adiponectin, the gene product of the adipose's most abundant gene transcript-1 (apM1) gene that is exclusively and abundantly expressed in white tissue; it is a 244-amino-acid protein with high structural homology to collagen VII, X, and complement C1q [22–25]. Although the physiological role of adiponectin is yet to be fully determined, experimental findings that this protein accumulates in injured vessels walls [26] and dose-dependently inhibits tumor necrosis factor (TNF)-α-induced cell adhesion in human aortic endothelial cells [27, 28] have led to the proposal that adiponectin may have an anti-atherogenic effect. Moreover, adiponectin has recently been reported to have an inhibitory effect on the proliferation of myelomonocytic progenitors and on phagocytic activity and TNF-α production by macrophages [29], findings consistent with an anti-inflammatory effect of this protein [30].

Previous studies demonstrated that reduced circulating adiponectin levels could be reversed partially after weight loss in obese and insulin-resistant subjects [31, 32]. Low concentration of adiponectin has also been associated with the reduction of the ability of insulin in phosphorylation of the insulin receptor, the beginning of insulin action [33].

Thus, weight loss is one of the most important factors for the metabolic improvement in obese individuals. The aim of this study is to demonstrate the difference between weight loss by diet restriction and surgery and the metabolic improvement over the insulin sensitivity, followed by the increasing of the adiponectin and GLP-1 levels, between two groups: a normal glucose tolerance (NGT) group and abnormal glucose metabolism (AGM) group.

Methods

Study Population

A total of 11 normal glucose-tolerant morbidly obese patients (NGT) (nine female/two male; BMI, 46.1± 2.27 kg/m^2) and eight AGM patients (seven female/one male; BMI, 51.20 kg/m^2; group AGM: four with type 2 diabetes and four impaired glucose tolerance) who were submitted to bariatric surgery and were invited to participate in this study. Exclusion criteria were hormonal replacement therapy, hepatic or renal insufficiency, stage 2 arterial hypertension according to the criteria of the Seventh Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure [34], and any pharmacological treatment that could influence insulin secretion and sensitivity. The investigation was approved by the Institutional Review Board of the School of Medical Science (University of Campinas), and all subjects gave informed consent before the study began.

Bariatric Surgery

The obese volunteers underwent Roux-en-Y gastric bypass (RYGBP) with silastic ring addition, which is based on a combination of restrictive plus malabsorptive mechanisms [35]. This surgery technique consisted of a 30-ml pouch vertically constructed on the lesser curvature of the stomach and separated from the rest of the stomach by stapling. A silastic ring band was placed loosely around the pouch ~2.0 cm from its distal point. Reconstruction was by Roux-en-Y gastro-jejunostomy with the jejunal limb measuring 150 cm.

Periods of the Study

Before Surgery This was the time when the patients were accepted into the group of surgery of the Faculty of Medical Sciences referred to as first evaluation (T1). The second moment was when the patients lost weight by dietary restriction and were ready for the RYGBP (T2).

After Surgery This period covers 9 months after the bariatric surgery (T3).

Experimental Protocol

All patients were examined in the morning after an overnight fast (~10–12 h). Body composition was evaluated by electrical bioimpedance with a biodynamic monitor (Biodynamics, Seattle, WA, USA) [36]. Arterial blood pressure was measured by a mercury sphygmomanometer with a large cuff. For the oral glucose tolerance test (OGTT), 75 g of glucose was ingested more than 5 min and venous blood sampled at 15 min at the first hour and sampled at 30 min over the last 2 h for determination of the glucose and insulin curve. GLP-1 was measured at time 0, 30, and 60 min of the OGTT. Adiponectin was measured at time 0 of the OGTT. Glucose tolerance was defined during the OGTT according to American Diabetes Association Criteria [37].

Analytical Procedures

Plasma glucose was measured by glucose oxidase technique in a Beckman Glucose Analyzer (Beckman, Fullerton, CA, USA). Serum concentration of insulin was measured by radioimmunoassay, by using specific kits for human insulin, from Linco Research (USA; <0.2% cross-reactivity with pro-insulin).The test sensitivity was 0.78 ng/ml. Serum GLP-1 was quantified by immunofluorescence, specific for humans, from Linco Research. The test sensitivity was 2 pM.

Data Analysis

Insulin secretion was evaluated from the OGTT. The total area under the time concentration curve (AUC) was calculated by trapezoidal rule [38].

The insulin sensitivity was evaluated by the homeostasis model assessment of insulin resistance (HOMA-IR), which was calculated by fasting glucose and fasting insulin (fasting insulin × fasting glucose)/22.5 [39, 40].

Statistical Analysis

For descriptive data, constant variables (mean, SE) were used for both groups during all periods. To compare data from both groups during the periods, ANOVA was used for repeated measure analysis, and when there was a statistical difference, the Tukey and contrast were used to identify the difference. All data are given as mean±SE. Statistical significance was considered when p value ≤0.05.

Results

Group Characteristics

The obese groups were paired by sex, age, and had a BMI of 46.1±2.27 and 51.20±4.6 kg/m^2 for NGT and AGM groups, respectively, and also had a high percentage of free fat mass for NGT group 43.11±1.52% and for AGM group 46.5±2.04% (Table 1). The BMI, waist, and percentage of free fat mass reduction were similar in both groups. The weight loss by diet restriction was ~10% for both groups and, 9 months after surgery, was 36.4±2.6% for the AGM group and 39.3±2.24% for the NGT group (Table 1).

Glucose Levels

At period T1, the glucose curve of the AGM group showed at the time 120 min levels 11.22±0.69 mmol/l and 6.54±0.31 mmol/l for the NGT group (Fig. 1). It was observed that both groups had a significant reduction in the glucose curve only 9 months after surgery (T3) when compared to T1 and T2. At the period T3, the curve of the AGM and NGT groups were similar and did not show any statistical

Table 1 Antropometric characteristic

Variables	Period	NGT	AGM
Sex		9 F, 2 M	7F, 1 M
BMI (kg/m^2)	T1	46.1±2.27[a]	51.20±4.6[a]
BMI (kg/m^2)	T2	41.77±2.07[a]	43.69±2.7[a]
BMI (kg/m^2)	T3	28.18±1.06[a]	31.97±1.8[a]
Waist (cm)	TI	130.57±3.8[a]	139.28±9.8[a]
Waist (cm)	T2	120.14±2.2[a]	127.17±7.03[a]
Waist (cm)	T3	96±2.67[a]	86.33±15.8[a]
%Total body fat mass	T1	43.11±1.53	46.50±2.04
%Total body fat mass	T2	43.06±1.55	43.68±2.05
%Total body fat mass	T3	27.01±1.80[b,c]	32.28±2.59[b,c]
%Total diet weight loss		10±1.95	12.3±2.49
%Total surgery weight loss		39.3±2.24	36.4±2.6

Data are expressed as means±SEM. *F* Female, *M* male, *NGT* group normal-glucose tolerance, *AGM* group abnormal-glucose metabolism, *T1* first evaluation, *T2* pre-surgery, *T3* 9 months after surgery

[a] T1 vs. T2 vs. T3, $p<0.001$

[b] T1 vs. T3, $p<0.001$, ANOVA for repeated measures

[c] T2 vs. T3, $p<0.001$, ANOVA for repeated measures

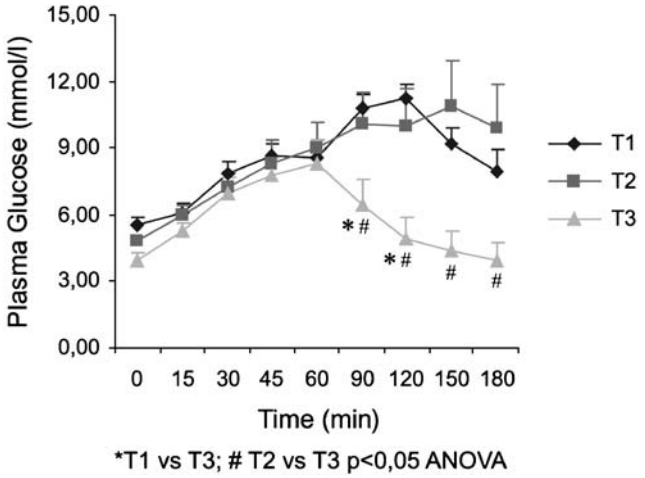

Fig. 1 Plasma glucose levels during OGTT for group AGM during periods T1, T2, and T3. *p<0.05, T1 vs. T3; #p<0.05, T2 vs. T3; ANOVA for repeated measure. Tukey test for statistic differences (*T1* first evaluation, *T2* pre-RYGBP, *T3* ninth after RYGBP)

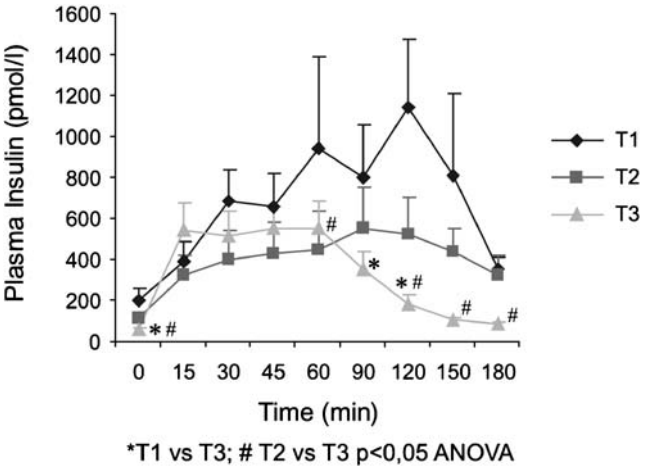

Fig. 3 Plasma insulin levels during OGTT for group AGM during periods T1, T2, and T3. *p<0.05, T1 vs. T3; #p<0.05, T2 vs. T3; ANOVA for repeated measure (*T1* first evaluation, *T2* pre-RYGBP, *T3* ninth after RYGBP)

difference at any point of the curve between AMG (Fig. 1) and NGT (Fig. 2).

Insulin Levels

Plasma insulin levels during the OGTT for AGM and NGT groups were measured at the periods T1, T2, and T3 (Figs. 3 and 4). Showing the same behavior as the glucose levels, the insulin levels changed from T1 to similar T3 in both groups, AGM (Fig. 3) and NGT (Fig. 4). The major reduction was at the first hour of the glucose load and fasting levels. At T1 after the glucose load, the first phase insulin secretion was not observed in both groups, showing a delayed insulin response. Only at T3, an improvement of the first phase of insulin secretion was noted.

GLP-1 Levels

GLP-1 levels, during the OGTT, are shown in Figs. 5 and 6. As can be seen, the curve of this peptide was similar for both groups at periods T1 and T2, but 9 months after surgery, at 30 and 60 min, the levels had significantly increased in both groups. It was observed that the AGM group (Fig. 5) had a higher secretion of GLP-1 at 30 min, which was 34.06±6.18 pmol/l, when compared to the NGT group, which was 22.69±4.04 pmol/l (Fig. 6), even though a statistical difference between both groups did not occur.

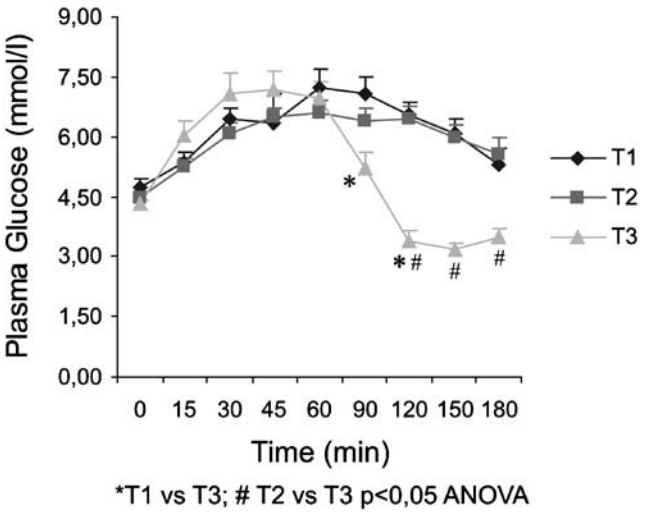

Fig. 2 Plasma glucose levels during OGTT for group NGT during periods T1, T2, and T3. *p<0.05, T1 vs. T3; #p<0.05, T2 vs. T3; ANOVA for repeated measure. Tukey test for statistic differences (*T1* first evaluation, *T2* pre-RYGBP, *T3* ninth after RYGBP)

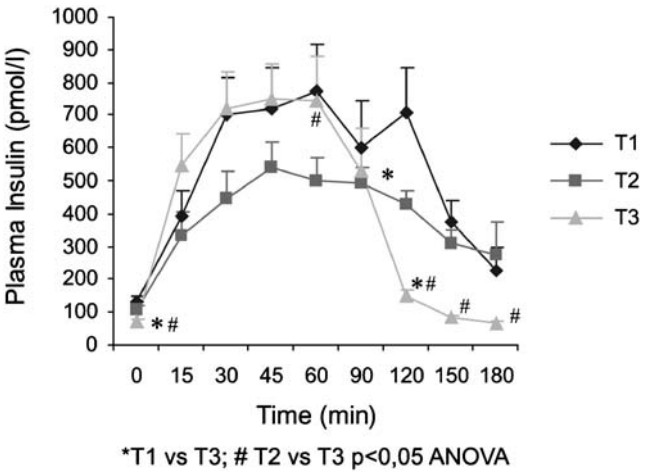

Fig. 4 Plasma insulin levels during OGTT for group NGT during periods T1, T2, and T3. *p<0.05, T1 vs. T3; #p<0.05, T2 vs. T3; ANOVA for repeated measure (*T1* first evaluation, *T2* pre-RYGBP, *T3* ninth after RYGBP)

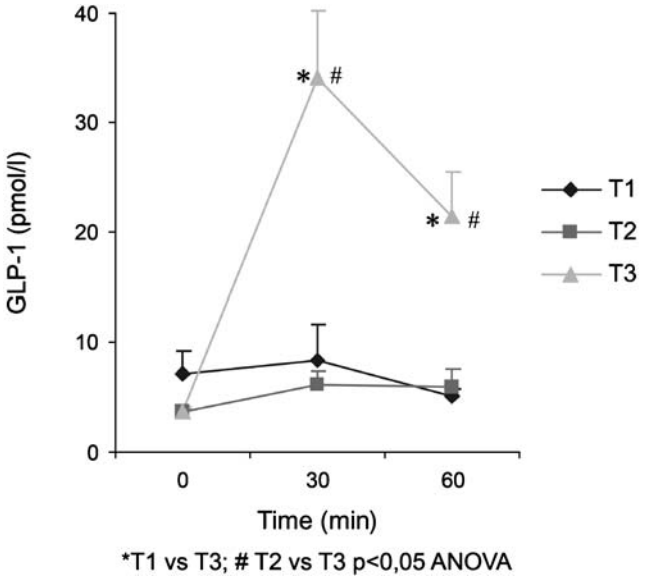

Fig. 5 GLP-1 levels during OGTT for group AGM during periods T1, T2, and T3. *$p<0.05$, T1 vs. T3; #$p<0.05$, T2 vs. T3; ANOVA for repeated measure (*T1* first evaluation, *T2* pre-RYGBP, *T3* ninth after RYGBP)

Insulin Sensitivity (HOMA-IR), AUC

In Table 2, it is shown that the values of HOMA-IR from NGT and AGM obese groups had a significant reduction at T3. However, there was no difference between the AGM and NGT groups.

It is observed in Table 2 (Figs. 3 and 4) that the fasting insulin levels increased 9 months after surgery (T3) when compared to T1 and T2, demonstrating the improvement of the first-phase insulin secretion, and this is also emphasized by the reduction of the area under the curve (Table 2). The fasting glucose levels did not show any difference during all periods or between groups.

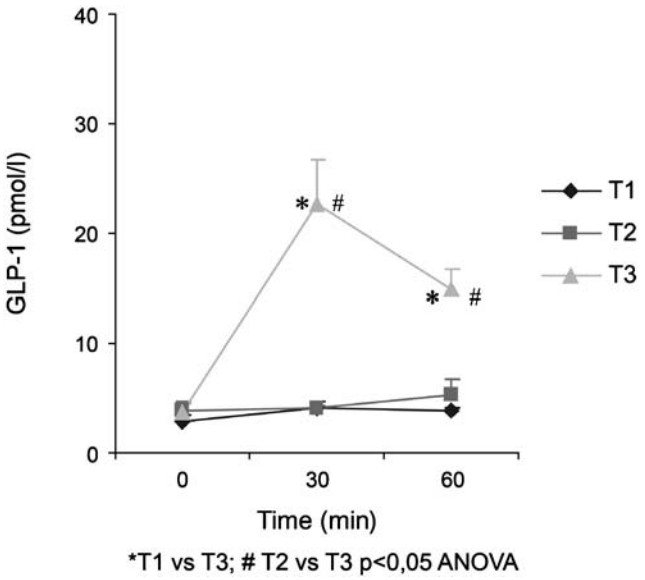

Fig. 6 GLP-1 levels during OGTT for group NGT during periods T1, T2, and T3. *$p<0.05$, T1 vs. T3; #$p<0.05$, T2 vs. T3; ANOVA for repeated measure (*T1* first evaluation, *T2* pre-RYGBP, *T3* ninth after RYGBP)

Table 2 OGTT data

Variables	Period	NGT	AGM
Fasting pl glucose (mmol/l)	T1	4.73±0.19	5.51±0.38
	T2	4.49±0.14	4.79±0.22
	T3	4.31±0.10	3.94±0.33
Fasting pl insulin (pmol/l)	T1	131.1±17.60	197.7±57.94
	T2	104.22±12.14	112.8±26.21
	T3	72.48±3.67*·**	61.2±9.33*·**
HOMA-IR	T1	4.71±0.76	9.58±3.67
	T2	3.70±0.54	4.67±1.34
	T3	1.97±0.35*·**	1.73±0.24*·**
Adiponectin (μg/ml)	T1	6.43±1.23	5.04±1.2
	T2	8.35±1.48	7.12±1.73
	T3	17.17±4.89*·**	15.43±5.52*·**
AUIC	T1	7,150.89±162.02	15,870.07±359.57
	T2	2,894.35±65.58	10,74.626±243.48
	T3	2,173.23±49.24*	3,304.22±74.86*

Data are expressed as mean±SEM.
AUIC Area under the insulin curve during OGTT
F Female, *M* male, *NGT* group normal-glucose tolerance, *AGM* group abnormal-glucose metabolism, *T1* first evaluation, *T2* pre-surgery, *T3* 9 months after surgery
*$p<0.05$, T1 vs. T3, ANOVA for repeated measures
**$p<0.05$, T2 vs. T3, ANOVA for repeated measures

Adiponectin Levels

Adiponectin increased its concentration levels for both groups before and after surgical weight loss. However, it did not have any statistical difference between periods T1 vs. T2. The difference was evidenced only 9 months after surgery (T3; Table 2).

Discussion

The improvement in the glucose metabolism in this current study is observed both in the patients from the AGM group and from the NGT group. Often, reductions are found in the doses of medicines for control of hyperglycemia in type 2 diabetic patients. Some studies show a total suspension of medication accompanying weight loss [41]. In agreement with these data, in this current study, it is observed that even if there was no stabilization of weight at the ninth month postoperatively, there was a significant reduction in the dosage of oral anti-diabetic medicines.

There were significant changes in plasma insulin and a decrease in the values of AUC of insulin during the weight loss by surgery (Table 2).

The metabolic improvement that occurred in the glucose and insulin metabolism can be attributed to the increase in insulin sensitivity, reduction of HOMA-IR, and improvement of adiponectin levels. Marin [42], in 2007, in postoperative morbidly obese patients, observed that the weight loss was associated with increased sensitivity to insulin and lowering of the basal secretion, which reached values similar to the control group, through the hyperinsulin clamp.

In our study, we used the calculation HOMA-IR, and a direct relationship was noted between weight reduction (decrease in BMI) and waist circumference and HOMA-IR reduction during the three periods in both groups; however, there was only a difference of periods T1 vs. T3 and T2 vs. T3, and this difference was significant after RYGBP. It should be emphasized that the individuals in the AGM group showed a major reduction in HOMA-IR and also in AUC of insulin, when compared with individuals in the NGT group (Table 2).

Adiponectin is referred to as an important mediator of the action of insulin and metabolism of glucose [43] through the activation of AMP kinase [44, 45]. Adiponectin presents anti-inflammatory effects by inhibiting the phagocytic activity and production of TNF-α by macrophages [46] and may be related to insulin sensitivity. Reduced levels of adiponectin were observed in obesity and type 2 diabetes and appear to be more related to the degree of insulin resistance than the fat and glucose levels, suggesting that low levels found in obesity and type 2 diabetes represent states of resistance to insulin [47]. The decrease of adiponectin can be justified by the fact that it is the only protein that is secreted by adipose tissue that has its expressions diminished in the states of obesity and type 2 diabetes.

Fruebis et al. [48] demonstrated that the administration of adiponectin in rats induced the weight loss, despite the maintenance of food intake. The mechanisms involved seem to be related to the reduction of circulating fatty acids and increase of lipid oxidation in muscle, thus improving insulin sensitivity. This same author in another study showed that improvement in blood glucose is associated with the reduction of the hepatic glucose release and increase of glucose uptake in muscle [48].

In the present study, we showed that adiponectin levels in morbidly obese individuals were diminished, and as the patients lost weight, these levels increased. However, there was no significant difference between adiponectin levels in periods T1 vs. T2, showing that the weight loss by dietary restriction (~10%) was not enough to promote metabolic changes. The difference between adiponectin levels only became clear 9 months after surgery, demonstrating that a large weight loss was necessary to improve adiponectin levels.

GLP-1 and Metabolic Improvement

GLP-1 has been reported as a potential mediator for the improvement in glucose tolerance because of its multiple benefits in the metabolism of glucose [49, 50], and it also has been shown that the weight loss observed after surgery was accompanied by the improvement of control of type 2 diabetes and increase in the levels of GLP-1 [21].

In a recent review regarding the effects of bariatric surgery on type 2 diabetes, Greenway et al. [51] pointed out that "the exact mechanism for the dramatic effect of surgical procedures for obesity on type 2 diabetes remains unknown." Among the possible hypotheses on the mechanisms responsible for the reversion of diabetes, the different effects of weight reduction, decreased caloric intake, and exclusion of food from transit in the hormonally active foregut were examined.

An even more attractive candidate mediator of the antidiabetic effects of RYGBP is GLP-1 because it exerts proliferative and anti-apoptotic effects on pancreatic beta cells [52]. It may also improve insulin sensitivity, at least indirectly [53]. Accordingly, methods to enhance GLP-1 signaling show great promise for the treatment of type 2 diabetes. Moreover, GLP-1 inhibits gastric emptying and can decrease food intake [54]. GLP-1 is secreted primarily by the hindgut after food ingestion, and part of this response results from direct contact between enteral nutrients and the intestinal L-cells that produce GLP-1. After RYGBP, ingested nutrients more rapidly reach the hindgut, bypassing part of the foregut and unimpeded by the pylorus. The larger postprandial bolus of nutrients in the hindgut should increase GLP-1 levels after RYGBP [55].

In our study, we showed that the increase in the levels of GLP-1 is significant in postoperative period T3 (ninth months) for both the NGT and AGM groups; improvement in insulin sensitivity was noted. Possibly, this increase in GLP-1 levels, together with the weight loss, inflammation reduction, and the surgical method, caused the metabolic improvement.

Moreover, the diet-restriction weight loss, ~10%, was unable to generate specific metabolic improvements for individuals, thus demonstrating that in degree III obese individuals, the RYGBP, because of the higher weight loss, is better related to metabolic improvement than diet-restriction weight loss.

We have demonstrated that surgical weight loss leads to improvement in the metabolism of carbohydrates by the improvement of insulin sensitivity, reducing type 2 diabetes. This improvement was also expressed for the improvement of adiponectin levels and GLP-1 levels. We emphasize that the degree of weight loss exerted great influence in the metabolic improvement. The AGM group showed normalization of the curve of glucose, insulin, improvement of

insulin sensitivity, and greater improvement in levels of adiponectin and increase of GLP-1, even though the group did not have weight stabilization.

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References

1. Bonadonna RC, Groop L, Kraemer N, et al. Obesity and insulin resistance in humans: a dose-response study. Metabolism 1990; 39:452–9.
2. Defronzo RA, Bonadonna RA, Ferranini E. A balanced overview. Diabetes Care. 1990;15:318–68.
3. Hostamisligil GS. Molecular mechanisms of insulin resistance and the role of adipocyte. Int J Obes. 2000;24:S23–7.
4. Park YW, Zhu S, Palaniappan L, et al. The metabolic syndrome: prevalence and associate risk factor finding in the US population from the Third National Health and Nutrition Examination Survey. Arch Intern Med. 2003;163:427–36.
5. Colditz G, Willet W, Rotniztky A, et al. Weight as a risk factor for clinical diabetes in women. Am J Epidemiol. 1990;132:501–13.
6. Pories WJ, Macdonald KG Jr, Morgan EJ, et al. Surgical treatment of obesity and its effect on diabetes: 10-y follow-up. Am J Clin Nutr. 1992;55:582S–5.
7. Residori L, Garcia-Lorda P, Flancbaum L, et al. Prevalence of co-morbidities in obese patients before bariatric surgery: effect of race. Obes Surg. 2003;13:333–40.
8. Buchwald H, Avidor Y, Brawnwald E, et al. Bariatric surgery: a systemic review and meta-analysis. JAMA 2004;2992:1724–37.
9. Blandine L, Stanley H, Krystle W, et al. Incretin levels and effect are markedly enhanced 1 month after Roux-en-Y gastric bypass surgery in obese patients with type 2 diabetes. Diabetes Care. 2007;30:1709–16.
10. MacDonald PE, El-kholy W, Riedel MJ, et al. The multiple actions of GLP-1 on the process of glucose-stimulated insulin secretion. Diabetes 2002;51:S434–42.
11. Creutzfedt W. The entero-insulinar axis in type 2 diabetes. Incretins as therapeutic agents. Exp Clin Endocrinol Diabetes. 2001;109:S288–303.
12. Egan JM, Meneilly GS, Haberner JF, et al. Glucagon-like peptide augments insulin-mediated glucose uptake in obese state. J Clin Endocrinol Metab. 2002;87:3768–73.
13. Valverde I, Villanueva-Penacarrillo ML, Malaisse WJ. Pancreatic and extrapancreatic effects of GLP-1. Diabetes Metab. 2002;28: 3S85–9.
14. Villanueva-Penacarrillo ML, Puente J, Redondo A, et al. Effect of GLP-1 treatment on GLUT2 and GLUT4 expression in NDDM and IDDM rats. Endocrine 2001;15:241–8.
15. Acitores A, Gonzáles N, Sancho V, et al. Participation of protein kinases in the stimulant action of GLP-1 upon 2-deoxy-D-glucose uptake by normal rat skeletal muscle. Horm Metab Res. 2005; 37:275–80.
16. Sancho V, Trigo MV, González N, et al. Effects of GLP-1 and exendins on kinase activity, 2-deoxy-D-glucose transport, lipolysis and lipogenesis in adipocytes from normal and streptozotocin-induced type 2 diabetic rats. J Mol Endocrinol. 2005;35:27–38.
17. Ruiz-Grande C, Alarcón C, Mérida E, et al. Lipolytic action of glucagon-like peptides in isolated rat adipocytes. Peptides 1992;13:13–6.
18. Perea A, Vinambres C, Clement F, et al. GLP-1 (7–36) amide effects on glucose transport and metabolism in rat adipose tissue. Horm Metab Res. 1997;9:417–21.
19. Villanueva-Penacarrillo ML, Márquez L, González N, et al. Effect of GLP-1 on lipid metabolism in human adipocytes. Horm Metab Res. 2001;33:73–7.
20. Nauck A, Heinesaat MM, Orskov C, et al. Preserved incretin activity of synthetic human gastric inhibitory polypeptide in patients with type 2 diabetes. J Clin Invest. 1993;91:301–7.
21. Blandine L, Stanley H, Krystle W, et al. Incretin levels and effect are markedly enhanced 1 month after Roux-en-Y gastric bypass surgery in obese patients with type 2 diabetes. Diabetes Care. 2007;30:1709–16.
22. Maeda K, Okubo K, Simomura J, et al. c-DNA cloning and expression of a novel adipose-specific collagen-like factor, *ap* M1 (adipose most abundant gene transcript 1). Biochem Biophys Res Commun. 1996;221:286–9.
23. Scherer PE, Williams S, Fogliano M, et al. A novel serum protein similar to C1q, produced exclusively in adipocytes. J Biol Chem. 1995;270:26746–9.
24. Hu E, Liang P, Spiegelman BM. AdipoQ is a novel adipose-specific gene dysregulated in obesity. J Biol Chem. 1996;18:10697–730.
25. Takahashi M, Arita Y, Yamagata K, et al. Genomic structure and mutations in adipose-specific gene, adiponectin. Int J Obes. 2000;24:861–8.
26. Okamoto Y, Arita Y Nishida M, et al. An adipocyte-derived plasma protein, adiponectin, adheres to injured vascular walls. Horm Metab Res. 2000;32:47–50.
27. Ouchi N, Kihara S, Arita T, et al. Novel modulator of endothelial adhesion molecules: adipocyte-derived plasma protein adiponectin. Circulation 1999;100:2473–6.
28. Ouchi N, Kihara S, Arita T, et al. Adiponectin, and adipocyte-derived plasma protein, inhibits NF-kb signaling through a cAMP-dependent pathway. Circulation 2000;102:1296–301.
29. Yokota T, Oritani K, Takahashi I, et al. Adiponectin, a new member of the family of soluble defense collagens, negatively regulates the growth of myelomonocytic progenitors and the function of macrophages. Blood 2000;96:1723–32.
30. Weyer C, Funahashi T, Tanaka S, et al. Hypoadiponectinemia in obesity and type 2 diabetes: Close association with insulin resistance and hyperinsulinemia. J Clin Endocrinol Metab. 2001;86:1930–5.
31. Yang WS, Lee WJ, Funahashi T, et al. Weight reduction increases plasma levels of an adipose-derived anti-inflammatory, adiponectin. J Clin Endocrinol Metab. 2001;86:3815–9.
32. Hotta K, Funahashi T, Arita Y, et al. Plasma concentrations of a novel, adipose–specific protein, adiponectin, in type 2 diabetic patients. Arterioscler Thromb Vasc Biol. 2000;20:1595–9.
33. Stefan N, Vozarova B, Funahashi T, et al. Plasma adiponectin concentration is associated with skeletal muscle insulin receptor tyrosine phosphorylation, and low plasma concentration precedes a decrease in whole-body insulin sensitvity in humans. Diabetes 2002;51:1884–8.
34. National Institutes of Health. The Seventh Report of Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (JNC VII). NIH Publication no. 03-5233. EUA, 2003; p. 2–3.
35. Fobi MAL, Lee H, Igwe D, et al. Revision on failed gastric bypass to distal Roux-en-Y gastric bypass: a review of 65 cases. Obes Surg. 2001;11:190–5.
36. Fulcher GR, Farrer M, Walker M, et al. A comparison of measurements of lean body mass derived by bioelectrical impedance, skinfold thickness and total body potassium. A study in obese and non-obese normal subjects. Scand J Lab Invest. 1991; 51:245–53.
37. American Diabetes Association. Report of the expert committee on the diagnosis and classification of diabetes mellitus. Clinical

practice recommendations 2003: committee report. The expert committee on the diagnosis and classification of diabetes mellitus. Diabetes Care. 2003;26(1):S4–20.
38. Potteiger JA, Jacobsen DJ, Donnelly JE. A comparison of methods for analyzing glucose and insulin areas under the curve following nine months of exercise in overweight adults. Int J Obes. 2002;26:87–9.
39. Mcauley KA, Williams SM, Mann JI, et al. Diagnosing insulin resistance in the general population. Diabetes Care. 2001;24: 460–4.
40. Matthews DR, Hosker JP, Rudenski AS, et al. Homeostasis model assessment, insulin resistance and beta cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 1985;28:412–9.
41. Sjostrom CD, Peltonem M, Wedel H, et al. Differentiated long-term effects of intentional weight loss on diabetes and hypertension. Hypertension 2000;36:20–5.
42. Marin, D. Resistência à insulina e função da célula beta: Efeito da perda de peso após bypass gástrico. PhD Thesis, Universidade Estadual de Campinas. Faculdade de Ciências Médicas; 2007.
43. Matsuzawa Y, Funahashi T, Nakamura T. Molecular mechanism of metabolic syndrome X: contribution of adipocytokines adipocyte-derived bioactive Substances. Ann NY Acad Sci. 1999;892: 146–54.
44. Tomas E, Tsao TS, Saha AK, et al. Enhanced muscle fat oxidation and glucose transport by ACRP 30 globular domain: a domain: acetyl- CoaA carboxylase inhibition and AMP- activated protein kinase activation. Proc Natl Acad Sci USA. 2002;99:16309–13.
45. Yamauchi T, Kamon J, Minokashi Y, et al. Adiponectin stimulates glucose utilization and fatty-acid oxidation by activating AMP-activated protein kinase. Nat Med. 2002;8:1288–95.
46. Yokota T, Oritani K, Takahashi I, et al. Adiponectin, a new member of the family of soluble defense collagens, negatively regulates the growth of myelomonocytic progenitors and function of the macrofages. Blood 2000;96:1723–32.
47. Weyer C, Funahashi T, Tanaka S, et al. Hypoadiponectinemia in obesity and type 2 diabetes: close association with insulin resistance and hyperinsulinemia. J Clin Endocrinol Metab. 2001;86: 1930–5.
48. Fruebis J, Tsao TS, Javorschi S, et al. Proteolytic cleavage product of 30-kDa adipocyte complement-related protein increases fatty acid oxidation in muscle and causes weight loss in mice. Proc Natl Acad Sci USA. 2001;98:2005–10.
49. Host JJ. On the physiology of GIP and GLP-1. Horm Metab Res. 2004;34:747–54.
50. Vilsboll T, Host JJ. Incretins, insulin secretion and type 2 diabetes mellitus. Diabetologia 2004;47:357–66.
51. Greenway SE, Greenway F, Klein S. Effects of obesity surgery on non-insulin-dependent diabetes mellitus. Arch Surg. 2002;137: 1109–77.
52. Drucker DJ. Glucagon-like peptide-1 and the islet ß-cell: augmentation of cell proliferation and inhibition of apoptosis. Endocrinology 2003;144:5145–8.
53. Zander M, Masdbad S, Madsen JL, et al. Effect of 6-week course of glucagon-like peptide 1 on glycemic control, insulin sensitivity, and ß-cell function in type 2 diabetes: a parallel-group study. Lancet 2002;359:824–30.
54. Drucker DJ. Enhancing incretin action for treatment of type 2 diabetes. Diabetes Care. 2003;26:2929–40.
55. Cummings DA, Overduin J, Fosyrt-Schubert K. Gastric bypass for obesity: mechanism of weight loss and diabetes resolution. J Clin Encrinol Metab. 2004;89:2608–15.