Overcoming metabolic syndrome in severe obesity: adiponectin as a marker of insulin sensitivity and HDL-cholesterol improvements after gastric bypass

Reversão da síndrome metabólica na obesidade mórbida: adiponectina como um marcador da sensibilização à insulina e do aumento do HDL-colesterol após o bypass gástrico

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ABSTRACT

Objective: To assess the relationship between adiponectin and metabolic parameters in severely obese women during surgical-induced weight loss. **Methods:** Nineteen lean (CT – BMI:21.2 ± 0.3 kg.m²), 14 overweight/class II obese (OB/OW – BMI: 29.7 ± 0.7 kg/m²) and 8 morbidly obese (OBIII – BMI: 56.4 ± 3.6 kg/m²) were evaluated by hyperinsulinemic-euglycemic clamp, adiponectin, and lipids. OBIII were evaluated at 5th and 16th month post-operatively. **Results:** Compared to lean, obese groups had lower adiponectin (OB/OW: 9.4 ± 0.9, OBIII: 7.1 ± 1.3 versus 12.2 ± 0.9 ng/dL; p < 0.01), lower HDL-cholesterol (OB/OW:1.05 ± 0.05, OBIII: 0.88 ± 0.04 versus 1.22 ± 0.07 mmol/L; p < 0.01) and insulin resistance-IR (glucose uptake, *M*-value – OB/OW: 43.6 ± 2.7, OBIII: 32.4 ± 3.2 versus 20.0 ± 1.8 umol/kgFFM.min; p < 0.001). Considering all subjects, adiponectin levels were inversely correlated to BMI and waist circumference, and directly to *M*-value and HDL-cholesterol (p < 0.01). During weight loss, improvements in IR (Study III: 36.1 ± 3.9 umol/kg/FFM.min, p < 0.0001), adiponectin (11.8 ± 1.4 ng/dL, p = 0.006) and HDL-cholesterol were observed (1.10 ± 0.04 mmol/L, p = 0.007). Moreover, HDL-cholesterol improvement was significantly and independently related to variations of adiponectin and BMI (r² = 0.86; p < 0.0002). **Conclusions:** The improvements of IR and adiponectin were related to surgical-induced weight loss, suggesting an important role of adiponectin in HDL-cholesterol regulation. Arq Bras Endocrinol Metab. 2009;53(2):293-300.

Keywords
Obesity; adiponectin; insulin resistance; weight loss; gastric bypass; HDL-cholesterol; glucose clamp technique

RESUMO

Objetivo: Identificar a relação entre adiponectina e parâmetros metabólicos em mulheres obesas mórbidas durante o emagrecimento por *bypass* gástrico. **Métodos:** Dezenove magras (CT – IMC: 21,2 ± 0,3 kg/m²), 14 com sobrepeso/obesidade classe II (OB/OW – IMC: 29,7 ± 0,7 kg/m²) e oito obesas classe III (OBIII – *IMC:56,4* ± 3,6 kg/m²) foram avaliadas pelo *clamp* euglicêmico-hiperinsulinêmico, adiponectina e lípides. OBIII submeteram-se aos mesmos testes no quinto e décimo-sexto mês pós-operatório. **Resultados:** comparados a CT, os grupos obesos tiveram menor adiponectinemia (OB/OW: 9,4 ± 0,9, OBIII: 7,1 ± 1,3 *versus* 12,2 ± 0,9 ng/dL; p < 0,01), menor HDL-colesterol (OB/OW: 1,05 ± 0,05, OBIII: 0,88 ± 0,04 *versus* 1,22 ± 0,07 mmol/L; p < 0,01) e resistência insulínica – RI (captação de glicose, *M* – OB/OW:43,6 ± 2,7, OBIII:32,4 ± 3,2 *versus* 20,0 ± 1,8 umol/kgFFM.min; p < 0,001). Analisando todos os voluntários: adiponectina correlacionou-se negativamente com IMC, circunferência da cintura e positivamente ao *M-clamp* e HDL-colesterol (p < 0,01). No emagrecimento, houve melhora da RI (Estudo III:36,1 ± 3,9 umol/kgFFM.min, p < 0,0001), adiponectina (11,8 ± 1,4 ng/dL, p = 0,006) e HDL-colesterol (1,10 ± 0,04 mmol/L, p = 0,007). Aumentos do HDL-colesterol foram significativa e independentemente relacionados às variações da adiponectina e IMC (r² = 0,86; p < 0,0002). **Conclusões:** A melhora da RI e adiponectina no emagrecimento induzido por *bypass* gástrico sugerem um importante papel da adiponectina na regulação do HDL-colesterol. Arq Bras Endocrinol Metab. 2009;53(2):293-300.

Descritores
Obesidade; adiponectina; resistência à insulina; perda de peso; derivação gástrica; colesterol HDL; *clamp* de glucose

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INTRODUCTION

Obesity is a major risk factor for the development of type 2 diabetes and for morbidity and mortality from cardiovascular disease (1), also considered as an insulin resistance state *per se* (2) and is a component of the metabolic syndrome. A central fat distribution, high triglycerides and low HDL-cholesterol are also included in metabolic syndrome definitions due to the high risk of this association (3,4). Adipose tissue, more than an energy pool, secretes many citokynes, including leptin, tumor necrosis factor-α (TNF-α), plasminogen activactor inhibitor type 1, IL-6 and adiponectin among others. Adiponectin is an adipose-specific protein expressed in and abundantly secreted from the white adipose tissue, with high structural homology to collagens VIII an X, and to complement C1q 11-14 and TNF-α (5). Adiponectin plasma levels are decreased in individuals with obesity, type 2 diabetes (6), coronary artery disease (7), hypertension and high-normal blood pressure (8) and also in first-degree relatives of type 2 diabetic patients (9). Although the physiological role of adiponectin is not yet fully determined, experimental studies have indicated that it has potential anti-atherogenic and anti-inflammatory properties (10,11). Additionally, circulating concentrations of adiponectin are closely related to whole-body insulin sensitivity (6) and were also demonstrated to be decreased in parallel to the progression of insulin resistance in Rhesus monkeys (12).

Low plasma adiponectin levels have been shown to be correlated with hypertriglyceridemia, low HDL-cholesterol and an increase in small dense LDL (13). This relationship is independent of age, sex, body mass index (BMI), diabetes and even insulin sensitivity (14-16). Sequentially, high adipodectinemia is associated with increased HDL (16). Adiponectin effect on HDL appears to be mediated by decreased HDL catabolism rather than higher synthesis (17,18) and inhibition of hepatic lipase activity (18).

Body weight reduction induced by diet or bariatric surgery is associated with improvement of insulin resistance (19-21), increase of HDL-cholesterol (16,20) and increase of adiponectin (16,20,23), apart from bariatric surgical technique (24,25). A correlation between HDL and adiponectin, apart from insulin sensitivity changes, has been found after weight loss through purely restrictive techinques (16).

To further characterization of the relationship between adiponectin and metabolic features of the insulin resistance in humans, we examined a cross-sectional association between plasma adiponectin concentration with HDL-cholesterol and with whole-body insulin sensitivity in non-diabetic lean, obese and severely obese women. Insulin sensitivity was assessed through the hyperinsulinemic euglycemic clamp, considered the gold standard pattern. In addition, a prospective evaluation was carried out in the group of severely obese subjects before and during weight loss induced by Roux-en-Y gastric bypass.

METHODS

Study population

Nineteen lean (CT group – BMI: 21.2 ± 0.3 kg.m²; aged 27 ± 2 years), 14 overweight or Class I or Class II obese women (OB/OW group – BMI: 29.7 ± 0.7 kg/m²; 54 ± 1 y) and eight severely obese women (OB III – BMI: 56.4 ± 3.6 kg/m²; 38 ± 4 y) were included in the study. All subjects had normal resting arterial blood pressure levels, and normal glucose tolerance test (OGTT) according to ADA criteria (26). None of them were taking any medication that could interfere in insulin sensitivity. All patients had normal liver and renal functional tests. The local ethical committee approved the study and a written informed consent was obtained from each subject.

After the initial metabolic studies (study I), the OBIII patients were submitted to a Roux-en-Y Gastric bypass with silastic ring (RYGB) surgery (27), that 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 of 6.2 cm was placed loosely around the pouch about 2.0 cm from its distal point. Reconstruction was by Roux-en-Y gastro-enterostomy with a jejunal limb measuring 150 cm and a biliopancreatic limb of 60 cm from the ligament of Treitz.

Experimental protocol

Body composition was evaluated by electrical bioimpedance using a biodynamics monitor. Arterial blood pressure was measured by mercury sphygmomanometer (a large cuff was used in obese individuals). Each patient and control subject underwent an oral glucose tolerance test (ingestion of 75 g glucose) and, with at least 1-week interval, insulin sensitivity was evaluated by means of a hyperinsulinemic euglycemic clamp. The

clamp study, which was done after an overnight fast (12 to 14 hours), consisted of 2 hours of euglycemic insulin infusion at a rate of 40 mU/min/m² of body surface area (28). A polyethylene, 20-gauge catheter was inserted into an antecubital vein for the infusion of insulin and glucose. Another catheter was inserted retrogradely into a wrist vein, and the hand placed in a heated box (~60° C) to allow the sampling of arterialized blood. During the insulin infusion, glucose was measured at intervals of 5 to 10 minutes and plasma glucose was maintained with a variable glucose infusion rate. Venous samples for insulin measurements were obtained at 20 minutes intervals, from 20 minutes before until 2 hours after starting insulin infusion.

Follow up: In the obese patients, the clamp study was repeated around the 4th month postoperative, Study II (weight loss of 17%), and again within weight-stable phase (stable weight for at least one month) around the 16th month, Study III (37% of weight loss).

Analytical procedures

Plasma glucose was measured by the glucose oxidase technique in a Beckman glucose analyzer during the clamp procedure (Beckman, Fullerton, CA). Plasma concentrations of insulin and adiponectin were measured by specific commercial kits (Linco Research Inc., St Louis, MO). Plasma uric acid, total cholesterol, LDL-cholesterol, HDL-cholesterol and triglycerides were assayed spectrophotometrically on an automatic colorimetric system (Cobas Miras-Roche).

Data analysis

Whole-body glucose utilization rate (M value) was calculated from the infusion rate of exogenous glucose (GIR) during the second hour of the insulin clamp period, after correction for changes in glucose levels in a distribution volume of 250 mL/kg. The M value was normalized per kg of fat-free mass (umol/kg FFM. min). The area under OGTT insulin curve was calculated by the trapezoidal rule.

Statistical analysis

All data are given as the mean ± s.e.m. Comparison of the lean control group (control) and obese patient's means at baseline (OBI) were performed by Mann-Whitney U test. ANOVA for repeated measures, Spear-

man and stepwise correlation analyses were calculated using standard techniques. A p value < 0.05 was required for statistical significance.

RESULTS

The anthropometric and metabolic variables for the control group and obese patients at baseline and after weight loss are shown in Table 1. The BMI of the obese group before the surgery was very high (56.4 ± 3.6 kg.m⁻²) and, in the last set of metabolic studies, it reached a mean value 35.7 ± 2.6 kg.m⁻² (Table 2). Fasting plasma glucose was similar among the groups (CT – 4.9 ± 0.1; OB/OW – 5.3 ± 1.4 and OBIII – 4.8 ± 0.11mmol/L). As expected, obese subjects displayed higher fasting plasma insulin and area under OGTT insulin curve (OB/OW – 116 ± 11 and OBIII – 164 ± 30 *versus* 69 ± 6 mmol/L 120 min; both p < 0.0001). Fasting plasma insulin decreased along weight reduction reaching levels that were similar to those of the control group.

Fasting plasma concentrations of adiponectin were lower in both obese groups, and increased to normal levels after the final weight loss (Tables 1-2). There were no significant differences in the fasting plasma levels of LDL-cholesterol, but HDL-cholesterol was reduced in obese women and, after weight loss (OB study III), increased to values that were similar to those of the control subjects. The variation of adiponectin levels in the third study as compared to before surgery was 89% ± 30% and that of HDL cholesterol was 26% ± 6%.

In the clamp studies, plasma glucose did not change during the insulin infusion. The plasma insulin levels reached during the steady state period were similar in control and both obese groups before surgery and even in the studies performed after weight loss. Insulin sensitivity was lower in the obese groups and improved in the follow-up period of class III obese group.

In the cross-sectional study, plasma adiponectin was positively and strongly related to HDL-cholesterol (Figure 1) and to insulin sensitivity (M_{ffm}), and negatively related to age, BMI, waist circumference, fat mass, fasting plasma insulin (FPI) and fasting plasma triglyceride (all p < 0.05) (Table 3). In a stepwise model including all the above variables, adiponectin was independently related to the waist circumference (r = 0.70; r² = 0.50; p < 0.0001). Insulin sensitivity, as expected, was also related to the above variables. HDL-cholesterol was not related to age, but to all the others (all p < 0.05). In

Table 1. Anthropometric characteristics and metabolic results in control subjects, overweight and obese patients before gastric bypass

	Control	OB/OW	Class III obesity
Number (F)	19	14	8
Age (years)	27 ± 2	54 ± 1 [c]	38 ± 4 [a]
Weight (kg)	57 ± 2	70 ± 2 [c]	152 ± 12 [c]
Body mass index (kg.m²)	21.2 ± 0.3	29.7 ± 0.7 [c]	56.4 ± 3.6 [c]
Fat mass (%)	19.6 ± 1.5	35.2 ± 0.9 [c]	47.0 ± 1.8 [c]
Adiponectin (ng/dL)	12.2 ± 0.9	9.4 ± 0.9 [b]	7.1 ± 1.3 [b]
Fasting plasma insulin (pmol/L)	82 ± 4	117 ± 11 [c]	259 ± 24 [c]
M_{ffm} (umol/kg FFM.min).	43.6 ± 2.7	32.4 ± 3.2 [c]	20.0 ± 1.8 [c]
LDL-cholesterol (mmol/L)	3.3 ± 0.2	3.1 ± 0.2	3.0 ± 0.2
HDL-cholesterol (mmol/L)	1.22 ± 0.07	1.05 ± 0.05 [b]	0.88 ± 0.04 [b]
Triglyceride (mmol/L)	0.71 ± 0.06	1.13 ± 0.10 [c]	1.57 ± 0.16 [c]
TG/HDL-cholesterol	0.61 ± 0.06	1.03 ± 0.28 [c]	1.86 ± 0.23 [b]

F = fasting; TG = triglyceride; M_{FFM} = M value from the steady state clamp period normalized by kilogram of fat-free mass; a = p ≤ 0.05; b = p ≤ 0.01; c = p ≤ 0.001 *versus* control group, Mann-Whitney analyses.

Table 2. Anthropometric and metabolic characteristics of Class III obese patients before and after weight loss induced by gastric bypass

	OB Study I	OB Study II	OB Study III	p
Number (F)	8	8	8	-
Age (years)	38 ± 4			
Peso (kg)	152 ± 12	127 ± 12 [c]	96 ± 9 [c]	< 0.0001
Body mass index (kg.m²)	56.4 ± 3.6	47.0 ± 3.6 [c]	35.7 ± 2.6 [c]	< 0.0001
BMI variation (%)		*-17 ± 2*	*-37 ± 1*	-
Fat mass (%)	47.0 ± 1.8	43.6 ± 1.9 [c]	33.8 ± 2.5 [c]	< 0.0001
Adiponectin (ng/dL)	7.1 ± 1.3	7.9 ± 1.2 [b]	11.8 ± 1.4	0.006
Adiponectin variation (%)		*26 ± 58*	*89 ± 30*	-
F. plasma insulin (pmol/L)	259 ± 24	129 ± 21 [b]	68 ± 10 [a]	0.0003
M_{ffm} (umol/kgFFM.min).	20.0 ± 1.8	25.4 ± 2.0 [b]	36.1 ± 3.9	< 0.0001
M_{ffm} variation (%)		*30 ± 7*	*129 ± 24*	-
LDL-cholesterol (mmol/L)	3.0 ± 0.2	2.9 ± 0.2	2.7 ± 0.2	NS
HDL variation (%)		*-3 ± 5*	*26 ± 6*	-
HDL-cholesterol (mmol/L)	0.88 ± 0.04	0.85 ± 0.05 [b]	1.10 ± 0.04	0.007
Triglyceride (mmol/L)	1.57 ± 0.16	1.55 ± 0.25 [b]	1.21 ± 0.18 [a]	0.01
TG/HDL-cholesterol	1.86 ± 0.23	2.19 ± 0.23 [b]	1.10 ± 0.16 [b]	0.009
TG/HDL-chol variation (%)		*5 ± 24*	*-55 ± 36*	-

F = fasting; TG: triglyceride; M_{ffm} = M value from the steady state clamp period normalized by kilogram of fat-free mass; NS = non-significant; p = ANOVA for repeated measures; a = p ≤ 0.05; b = p ≤ 0.01; c = p ≤ 0.001 *versus* control group (Table 1), Mann-Whitney analyses.

a stepwise model including adiponectin, age, BMI, fat mass, fasting plasma insulin and triglycerides, the main variable related to HDL-cholesterol also was the waist circumference (r = 0.66; r² = 0.43; p < 0.0001).

In the follow-up of morbidly obese patients, adiponectin, insulin sensitivity and HDL-cholesterol results were related to the same variables observed in the cross-sectional study (all p < 0.05; data not shown). In addi-

tion, the M_{ffm} improvement, assessed as percent variation of the studies II and III relative to the Study I, was related to the variations of BMI (r = -0.77; p = 0.003), fat mass (r=-0.70; p=0.007) and HDL-cholesterol (r = 0.63; p = 0.02) and not to the adiponectin variation. By stepwise analysis including these variables, M_{ffm} was independently related only to the fat mass variation (r = 0.71; r² = 0.47; p = 0.002). Meanwhile, HDL decrease was
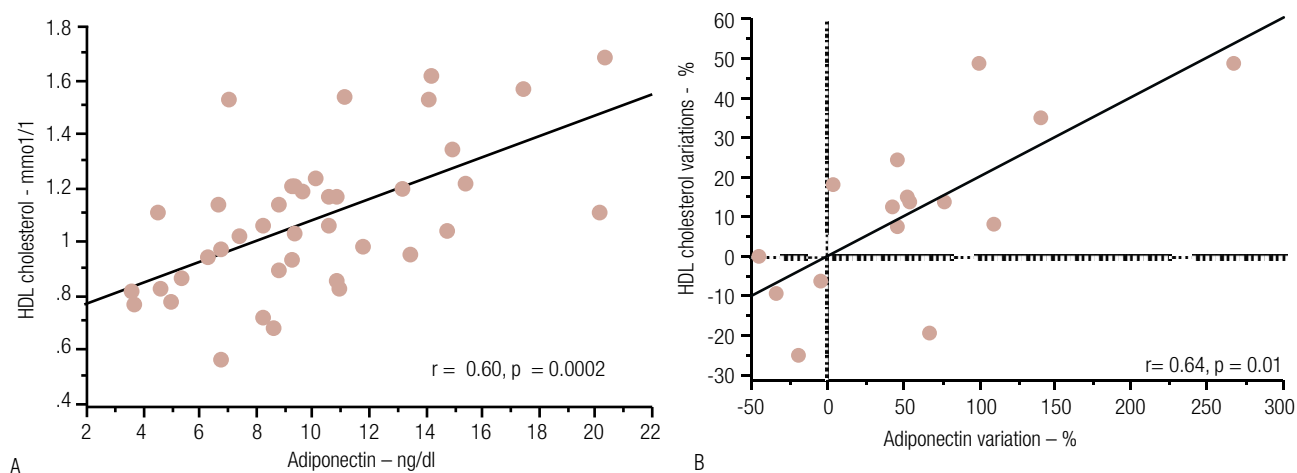
Figure 1. (A) Simple linear regression between plasma adiponectin and HDL-cholesterol in the pooled data of the obese patients in the cross-sectional data; **(B)** Simple linear regression between variations of plasma adiponectin and of HDL-cholesterol in the Class III obese patients after gastric bypass (Study II and III variations *versus* Study I).

Table 3. Relationship between adiponectin and metabolic and anthropometric variables in the pooled data of Control, OB/OW and class III obese patients before the surgery

	Adiponectin		M		HDL	
	r	p	r	p	r	p
Age	-0.30	0.05	-0.36	0.02	NS	NS
BMI	-0.49	0.002	-0.79	< 0.0001	-0.47	0.003
Waist	-0.51	0.001	-0.82	< 0.0001	-0.57	0.0006
Fat mass (kg)	-0.44	0.004	-0.76	< 0.0001	-0.46	0.004
F plasma insulin	-0.64	< 0.0001	-0.76	< 0.0001	-0.41	0.01
F plasma triglyceride	-0.35	0.03	-0.64	0.0001	-0.39	0.02
HDL-cholesterol	0.60	0.0002	0.38	0.02	-	-
TG/HDL-cholesterol	-0.50	0.0003	-0.59	0.0005	-	-
M_{ffm}	0.52	0.0008	-	-		

BM = body mass index; F = fasting; TG = triglyceride; M_{ffm} = M value from the steady state clamp period normalized by kilogram of fat-free mass; r = coefficient and p value from the Spearman Signed Rank correlation; NS = non-significant.

related to the changes of BMI (r = -0.83; p = 0.001), fat mass (r = -0.69; p = 0.008) and adiponectin (r = 0.64; p = 0.01). In a stepwise model including BMI, fat mass and adiponectin variations, HDL-cholesterol variation remained independently related to both BMI and adiponectin changes (r = 0.86; r^2 = 0.74; p = 0.0002). The ratio Triglyceride/HDL-cholesterol was calculated as an index to assess the presence of small dense LDL. This ratio was higher in obese subjects (Table 1), was related to M_{ffm} and to adiponectin, and it decreased along weight loss (Table 2).

DISCUSSION

The present study was carried out to test the hypothesis that adiponectin is independently associated with features of insulin resistance syndrome, specially the lipid profile, during a weight-loss program. Our results demonstrated that adiponectin is reduced in obese women and increases after the weight loss induced by gastric bypass. Additionally, in the present study, it was observed an association of HDL-cholesterol and adiponectin in lean and obese subjects before gastric bypass in lean and obese subjects without any associated disease and, during the follow-up, the increase of HDL-cholesterol was directly related to the adiponectin increase, and inversely to the amount of weight loss.

Previous studies using hyperinsulinemic euglycemic clamp have reported that the degree of hypoadiponectinemia is closely related to the degree of insulin resistance (5,9,15,16). In our study, the main correlate of adiponectinemia in the cross-sectional data was the waist circumference (a marker of intra-abdominal fat), confirming previous results (15) and the importance of

central fat distribution. In the follow-up, this correlation was not tested due to the difficult to adequately measure waist in patients after marked weight loss in whom important anatomical changes in the abdomen have occurred. Adiponectin was also directly related to intra-abdominal fat area (15), but we could not measure the visceral fat with some accurate method (for example tomography) because of the machine limitation for weight.

Weight loss in severe obesity determines a reduction in insulin resistance in subjects with normal glucose tolerance (19,20,22) as well as in diabetic patients, with positive impact on metabolic parameters including the diabetic control (20,29). Most reports have shown that plasma adiponectin levels increase with weight reduction (16,22,23); discordant results may be attributed to a shift in the pattern of adiponectin oligomers towards the higher molecular weight forms, which are not apparent to current assays of total adiponectin (30,31). The increase in the adiponectin plasma levels was low in the study II, when the mean weight loss was about 30 kg, corresponding to about 17% of BMI reduction and reached levels comparable to those of CT group in the study III (-37% of BMI and +89% of adiponectin *versus* before surgery). Here, we also report a correlation between weight loss and increases in insulin sensitivity and in adiponectin levels, but the increase in insulin sensitivity was not independently related to adiponectin. However, we cannot exclude that the small sample of obese patients evaluated after bariatric surgery may be the cause of the lack of a significant relationship between weight loss-induced decrease in insulin resistance and the increase in plasma adiponectin.

It is interesting to point out that the changes and associations observed during weight loss in obese patients reproduce the findings of the cross-sectional pooled data of obese and lean subjects. So, our results in both analyses are consistent with the notion that adiponectin plays a role in the HDL-cholesterol control in humans. Otherwise, a recent work has shown a correlation between adiponectin and HDL independently of the degree of adiposity (32). Vergès and cols. (18) found that adiponectin may have direct relation with HDL catabolism, independently of obesity and insulin resistance. Even so, correlation among variables does not definitively confirm a causal relationship. The increases of adiponectin and HDL-cholesterol, along with weight loss, were strongly and independently correlated, suggesting some common physiological/pathological

mechanism. Through the known pathways adiponectin may modulate HDL (decreased catabolism and inhibition of hepatic lipase activity), some scenarios do not support direct causality. Plasma lipids or lipoproteins are not influenced by adiponectin gene overexpression (33) or deletion (34) in mouse models. Fibrates and niacin, drugs that primarily lower triglycerides and increase HDL level, increase plasma adiponectin levels in patients with cardiovascular disease, dyslipidemia, and metabolic syndrome proportionally to the extent of change in HDL and triglycerides levels (35-37).

Fibrates and thiazolidinediones (TZDs) are synthetic ligands of nuclear receptors called peroxisome proliferator-activated receptors, PPAR-α and PPAR-γ respectively. TZDs increase both HDL and adiponectin concentrations (38); adiponectin levels have been considered a biomarker of in vivo PPARγ activation. Adiponectin enhancement by fibrates is achieved (at least) partly through PPA-α activation (37) and niacin indirectly stimulates the PPAR system (35).

PPARs are involved in the regulation of lipid and carbohydrate metabolism and adipogenesis and are thought to function as sensors for dietary fatty acids and their metabolic derivatives. Beyond weight loss and hormonal interactions, it is reasonable to speculate that bariatric surgery may affect the way dietary ligands are delivered to PPAR-expressing tissues.

High concentration of small dense LDL (sdLDL) is another lipid disorder related to hipoadiponectinemia (13). The major contributor to its formation in the plasma seems to be an increased hepatic lipase and decreased lipoprotein lipase activities, both associated to low adiponectinemia (the latter contributes for larger, triglyceride-rich LDL, a substrate for the hepatic lipase) (13). These particles were not measured in this study, so we tested the ratio of triglycerides/HDL-cholesterol, reported as a marker of small dense LDL particles (39). This variable was higher in the obese groups and markedly decreased after weight loss, but this response was uniform only in the third study when the amount of weight loss was very high. The same time course was observed to the HDL and adiponectin improvements. Possibly, in these morbidly obese patients, an important weight loss is required to significantly improve the lipid profile and the adiponectin levels and action. It is also important to observe that even if the insulin sensitivity increased approximately 30% in the second study, it means an increase in glucose uptake of 5 umol/kg$_{FFM}$.min, the patients being strongly insulin resistant yet.

However, in the third study the improvement in insulin resistance was important, following a time-course similar to the lipid profile.

Higher levels of adiponectin are associated with a lower cardiovascular risk. It may be partially explained by its effects on lipid metabolism, particularly through HDL-cholesterol (by removing cholesterol from foam cells, by inhibiting the oxidation of LDL and by anti-inflammatory and antithrombotic properties) (40). Furthermore, adiponectin is an independent cardiovascular marker in diseases and has direct positive effects in the endothelium (endothelial dysfunction and infiltration, plaque instability) and in the myocardium (pathological cardiac remodeling and ischemic injury) effects (7,10,11).

In summary, in lean and obese women without associated diseases, plasma HDL-cholesterol is independently associated with plasma adiponectin. During weight-loss induced by gastric bypass, this relationship is maintained. Our present data suggests that weight loss, reduction in insulin resistance, increase in adiponectin plasma concentrations and the interaction with the improvement of the lipid profile can have a positive effect against atherosclerosis. Therefore, any measure that could be taken to increase adiponectin may be beneficial.

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