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Type 2 diabetes mellitus is characterized by reduced postprandial adiponectin response: a possible link with diabetic postprandial dyslipidemia

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Abstract

We investigated postprandial plasma and adipose tissue (AT) adiponectin changes in relation to obesity and type 2 diabetes mellitus. Fasting and 6 hours after a standard fat-rich meal blood samples (adiponectin, glucose, insulin, lipids) and needle biopsies of abdominal subcutaneous AT (adiponectin messenger RNA, lipoprotein lipase activity) were taken in 10 obese diabetic (OD), 11 obese nondiabetic (OND), and 11 normal-weight control (C) men. The OD and OND subjects had similar adiposity (body mass index, waist circumference) and insulin resistance (hyperinsulinemic euglycemic clamp). Fasting plasma adiponectin and AT gene expression were not significantly different between groups. After meal, plasma adiponectin decreased in OD but significantly increased in OND and C, the changes being significantly different between groups (analysis of variance, $P = .01$); adiponectin messenger RNA decreased in OD (-0.27 ± 0.25 AU, $P = .01$) but was unchanged in OND ($P = .59$) and C ($P = .45$). After meal, plasma adiponectin correlated inversely with triglyceride and cholesterol concentrations in chylomicrons and large very low-density lipoprotein, and directly with AT lipoprotein lipase activity ($P < .05$ for all). Type 2 diabetes mellitus is associated with lower postprandial plasma levels and AT gene expression of adiponectin independently of degree of adiposity and whole-body insulin sensitivity. In patients with diabetes, this may exacerbate postprandial abnormalities of lipoprotein metabolism.

1. Introduction

Adiponectin is the most abundant cytokine produced in adipose tissue, playing a relevant role in glucose and lipid metabolism [1]. In particular, plasma concentrations of adiponectin are positively correlated with insulin sensitivity, especially in obese individuals [2,3]. Moreover, lower adiponectin levels are often found in individuals with insulin resistance and in patients with type 2 diabetes mellitus [4,5]. In addition, adiponectin has been associated with a lower cardiovascular risk [6]; and its potential role in the treatment of coronary heart disease has been suggested [7].

Despite this potential pathophysiologic and clinical relevance, very little is known about the regulation of circulating adiponectin levels in humans, particularly as related to the effects of food intake. In Western societies, most of the daytime is in the postprandial state. Therefore, adiponectin changes after a meal could have relevant implications because the postprandial condition brings about major metabolic perturbations, including the changes in plasma insulin levels related to adiponectin. Moreover, it influences cardiovascular risk, which is increased by postprandial dyslipidemia [8] and hyperglycemia [9].

Few and very controversial results have been reported so far in relation to the effects of food intake on adiponectin levels. The results of the first study that showed an early plasma adiponectin increase after meal in morbidly obese but not in lean subjects [10] were not confirmed in another

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study where no significant changes were observed 3 hours after a similar meal in either morbidly obese or control subjects [11]. The authors of the first study also failed to reproduce their results in completely similar conditions [10,12]. In the latter report, the authors also studied patients with type 2 diabetes mellitus, on diet alone or treated with metformin, and did not find significant postprandial adiponectin changes.

These inconsistencies may arise from differences in meal composition, as well as in the population examined, because the metabolic status of an individual could induce different postprandial response. In addition, the postprandial period investigated could have been too short to detect a different postprandial behavior after a fat-rich meal, especially in individuals with type 2 diabetes mellitus, who have a typical delayed lipemic response after meal. In this respect, it is not known whether adiponectin response to a meal is related to postprandial lipid metabolism. Such relation may be envisaged on the basis of the crucial role played by adipose tissue in the disposal of the fat contained in a meal [13]. Moreover, similar to low adiponectin levels, postprandial lipid abnormalities are associated with insulin resistance, type 2 diabetes mellitus, and atherosclerosis [8,14,15].

The link between adiponectin and lipid metabolism might be represented by lipoprotein lipase (LPL). An association was found between plasma adiponectin levels and activity of LPL, a key enzyme in intravascular lipolysis and in postprandial lipid metabolism [16]. In that study, LPL activity in postheparin plasma was related to plasma adiponectin levels in both nondiabetic men and patients with type 2 diabetes mellitus.

Therefore, the aims of our study were to evaluate whether (*a*) adiponectin plasma level and adipose tissue gene expression are acutely influenced by meal ingestion, (*b*) meal-related effects differ according to metabolic status (insulin resistance or type 2 diabetes mellitus), and (*c*) postprandial adiponectin changes are related to postprandial lipemia and adipose tissue LPL changes.

2. Methods

2.1. Subjects

Ten patients with type 2 diabetes mellitus and obesity, 11 patients with obesity only, and 11 normal-weight control subjects, all men, participated in the study. Their baseline characteristics are shown in Table 1. Diabetes was diagnosed according to the American Diabetes Association criteria [17]. All subjects had normal fasting plasma concentration for both triglyceride (<1.7 mmol/L) and cholesterol (<5.5 mmol/L). The subjects had no history or symptoms of any known disease, apart from diabetes; nor were they vegetarians or engaged in intensive physical activity. They were not taking any hypolipidemic drug. Diabetic patients were in stable glycemic control on diet alone (hemoglobin A_{1c} = 6.5 ± 0.5%). The study protocol was approved by the Federico II University Ethics Committee, and informed consent by the participants was obtained.

Table 1
Physical characteristics, fasting plasma lipid concentrations, and insulin sensitivity measures of the subjects participating in the study

	Diabetic obese	Obese	Controls
Male (n)	10	11	11
Age (y)	45.6 ± 6.4	45.8 ± 8.7	39.1 ± 8.3
Body mass index (kg/m^2)	32.8 ± 2.0†	34.5 ± 2.7†	24.0 ± 1.3
Waist circumference (cm)	112 ± 8†	113 ± 7†	85 ± 4
Plasma cholesterol (mmol/L)	4.51 ± 0.63	4.87 ± 0.91	4.16 ± 0.62
Plasma triglycerides (mmol/L)	1.17 ± 0.27	1.12 ± 0.39	0.88 ± 0.31
Plasma HDL cholesterol (mmol/L)	0.91 ± 0.10*	1.11 ± 0.28	1.21 ± 0.25
Glucose infusion rate during clamp (*M*) (mg kg^{-1} min^{-1})	4.1 ± 0.9†	4.5 ± 1.5†	8.2 ± 2.2
M/*I*	2.1 ± 1.1†	1.7 ± 0.8†	7.5 ± 3.2

Data are means ± SEM.
* $P < .05$ vs controls.
† $P < .001$ vs controls.

2.2. Experimental procedures

In the morning after at least a 12-hour fast, anthropometric measurements were taken, according to standardized procedures; subjects were then administered a standard meal. Before the meal and 6 hours thereafter, blood samples were taken to determine plasma levels of glucose, insulin, adiponectin, and lipoproteins. Thereafter, a needle biopsy of abdominal subcutaneous adipose tissue was taken for the determination of adiponectin messenger RNA (mRNA) and LPL activity. A similar biopsy on the opposite side of the lower abdomen was also made on a different day in fasting conditions. On that same day, subjects underwent a hyperinsulinemic euglycemic clamp.

For 3 days before investigations, subjects were asked to limit physical activity.

2.2.1. Standard test meal

The meal consisted of a pie made of mashed potato, whole milk, egg, cheese, ham, and butter, which was ingested in about 15 minutes. The meal, which provided 944 kcal, was composed of 31% carbohydrates, 57% fat (34% saturated fat), and 12% protein.

2.2.2. Hyperinsulinemic euglycemic clamp [18]

Regular insulin was administered intravenously at a constant rate of 1.5 mU per kilogram of body weight per minute for 2 hours. Blood glucose concentrations were maintained at around 5.0 mmol/L by adjusting glucose infusion rate according to blood glucose measurements on an AccuChek analyzer (Roche, Basle, Switzerland). Mean glucose infusion rate during the last 30 minutes of the clamp (*M* value) and *M*/*I* ratio (*M* value divided by the corresponding plasma insulin concentrations) were calculated as measures of whole-body insulin sensitivity.

2.2.3. Lipoproteins

Fasting and postprandial lipoprotein subfractions were isolated by discontinuous density gradient ultracentrifugation as previously described [14]. Ultracentrifugation was carried out in a Beckman SW 40-Ti rotor on a Beckman Optima L-90K ultracentrifuge (Beckman Instruments, Fullerton, CA). Briefly, 3 consecutive runs were performed at 15°C and at 40 000 rpm to float chylomicrons (Svedberg flotation unit [Sf] >400), large very low-density lipoprotein (VLDL) (Sf 60-400), and small VLDL (Sf 20-60); intermediate-density lipoprotein (Sf 12-20) and low-density lipoprotein (Sf 0-12) were recovered from the gradient after the Sf 20 to 60 particles had been collected; high-density lipoprotein (HDL) was isolated by a precipitation method.

2.2.4. Adipose tissue LPL activity

Lipoprotein lipase heparin-releasable activity was determined as previously described [19]. Briefly, 5 to 10 mg frozen adipose tissue was incubated in a buffer containing beef lung heparin. Thereafter, 100 μL of eluate was incubated with 100 μL ^{3}H-trioleoylglycerol substrate emulsion. The ^{3}H-labeled oleic acid released was extracted and counted in a Wallac 1410 Liquid Scintillation Counter (Perkin-Elmer, Shelton, CT).

2.2.5. Adipose tissue adiponectin gene expression

Messenger RNA expression of adiponectin was evaluated by reverse transcriptase polymerase chain reaction (PCR). Briefly, RNA extraction, first-strand complementary DNA synthesis, and PCR condition were obtained as previously described [19,20]. The specific primers to amplify adiponectin (Acc.XM-003191) and glyceraldehyde-3-phosphate dehydrogenase (GAPDH) (NM_002046) were as follows: adiponectin, sense 5′-TGT TGC TGG GAG CTG TTC TAC TG-3′ and antisense 5′-ATG TCT CCC TTA GGA CCA ATA AG-3′(238–base pair product); GAPDH, sense 5′-AGG TGA AGG TCG GAG TCA ACG-3′ and antisense 5′-GCT CCT GGA AGA TGG TGA TGG-3′ (231–base pair product). Reaction conditions were standardized to observe a linear amplification of PCR products. Analysis of all PCR products, electrophoresed on agarose gel, was performed by densitometric gel scanning using the Gel Doc 2000 video image system (Bio-Rad Laboratories, Hercules, CA). Results are expressed as the ratio between the adiponectin gene and GAPDH in each sample analyzed [21].

2.2.6. Other measurements

Plasma adiponectin concentrations were assayed in plasma stored at −80° using a competitive enzyme-linked immunosorbent assay (BioVendor Laboratory Medicine, Brno, Czech Republic). The assay limit is 100 mg/L, and the sensitivity (detection limit) is 0.2 mg/L. The intra- and interassay coefficients of variation were 8.4% and 7.6 %, respectively. Cholesterol and triglyceride concentrations were assayed by enzymatic colorimetric methods (Roche Diagnostics, Milan, Italy). Plasma insulin concentrations were measured by enzyme-linked immunosorbent assay (Technogenetics, Milan, Italy).

2.3. Statistical analysis

Data are expressed as mean ± SEM, unless otherwise stated. Differences between the 3 groups (diabetic obese, obese, and control) were evaluated by analysis of variance (ANOVA) and by post hoc test between groups (least significant difference). Differences between baseline and after-meal values were evaluated by paired t test. Variables not normally distributed were analyzed after logarithmic transformation or by nonparametric tests. Two-tailed tests were used, and a $P < .05$ was considered statistically significant. Statistical analysis was performed according to standard methods using the Statistical Package for Social Sciences software (SPSS/PC; SPSS, Chicago, IL).

3. Results

3.1. Anthropometrics

Obese subjects with and without diabetes had similarly high body mass index (32.8 ± 2.0 and 34.5 ± 2.7 kg/m^2) and abdominal circumferences (112 ± 8 and 113 ± 7 cm) as compared with lean controls (24.0 ± 1.3 kg/m^2 and 85 ± 4 cm, $P < .001$ for all) (Table 1).

3.2. Whole-body insulin sensitivity

Glucose infusion rate during the last 30 minutes of the hyperinsulinemic euglycemic clamp (M value) was similarly lower in the 2 obese groups as compared with normal-weight controls ($P < .001$ for both, Table 1). The impairment in insulin sensitivity was more evident when M values were corrected for the concomitant plasma insulin levels and expressed as M/I ratio.

3.3. Plasma glucose and insulin

As expected, blood glucose levels were significantly higher in diabetic subjects both at fasting and after the meal compared with the other 2 groups. Fasting and postprandial plasma insulin levels were significantly higher in both groups of obese with and without diabetes as compared with controls (Table 2).

3.4. Plasma adiponectin

Fasting plasma adiponectin concentrations were not significantly different between the groups (3.3 ± 0.3, 4.5 ± 0.8, and 4.7 ± 0.8 mg/L in obese diabetic, obese, and control subjects, respectively) (Fig. 1). Six hours after the meal, differences between the groups were statistically significant, the concentrations being lower in diabetic obese than in nondiabetic obese and control subjects (ANOVA, $P = .022$). Compared with fasting, plasma adiponectin concentrations were significantly increased 6 hours after the meal in control ($P = .033$) and obese subjects ($P = .026$), whereas there were

Table 2
Fasting and postprandial metabolic parameters in diabetic obese, obese, and control subjects

		Diabetic obese	Obese	Controls
Plasma glucose (mmol/L)	Fasting	7.3 ± 2.0*,†	5.0 ± 0.5	4.8 ± 0.5
	6 h	5.8 ± 0.4*,†,‡	4.5 ± 0.1	4.6 ± 0.1
Plasma insulin (pmol/L)	Fasting	95.9 ± 15.7*	97.5 ± 12.7*	39.4 ± 6.1
	6 h	104.2 ± 18.8*	98.3 ± 12.2*	35.2 ± 6.1
Chylomicron triglycerides (μmol/L)	Fasting	38 ± 11	50 ± 10	22 ± 7
	6 h	312 ± 82†,‡	131 ± 19‡	187 ± 59‡
Chylomicron cholesterol (μmol/L)	Fasting	4.8 ± 1.6	5.2 ± 0.8	3.8 ± 1.1
	6 h	30.7 ± 7.3*,†,‡	14.9 ± 1.8‡	16.6 ± 4.0‡
Large VLDL triglycerides (μmol/L)	Fasting	532 ± 78	505 ± 92	384 ± 71
	6 h	944 ± 154*,‡	683 ± 131‡	438 ± 55
Large VLDL cholesterol (μmol/L)	Fasting	159 ± 27	154 ± 36	122 ± 26
	6 h	306 ± 53*,‡	233 ± 56‡	123 ± 21
Adipose tissue LPL activity (nmol fatty acids g^{-1} h^{-1})	Fasting	102 ± 16*,†	231 ± 41	327 ± 98
	6 h	102 ± 21*,†	212 ± 34	267 ± 44

Data are means ± SEM.
* $P < .05$ vs controls.
† $P < .05$ vs obese.
‡ $P < .05$ vs fasting.

no statistically significant changes in diabetic subjects ($P = .21$) (Fig. 1). The changes 6 hours postmeal *minus* fasting were significantly different between the groups (ANOVA, $P = .01$).

3.5. Adiponectin adipose tissue gene expression

Fasting adiponectin mRNA levels in adipose tissue were not significantly different between the 3 groups (1.3 ± 0.2, 1.4 ± 0.3, and 1.2 ± 0.1 AU in diabetic obese, obese, and control subjects, respectively) (Fig. 2). Compared with fasting, adiponectin mRNA levels decreased 6 hours after the meal in diabetic obese subjects ($P = .01$), whereas they did not change significantly in obese ($P = .59$) and control ($P = .45$) subjects (Fig. 2).

3.6. Postprandial lipoproteins

Diabetic subjects had higher levels of postprandial chylomicron lipids compared with the other 2 groups, the differences being significant 6 hours after the meal for both triglycerides and cholesterol ($P < .05$ vs obese) (Table 2). Triglyceride and cholesterol concentrations in large VLDL increased significantly 6 hours after the meal in both diabetic obese and simply obese groups and were significantly higher than those in controls (Table 2).

3.7. Adipose tissue LPL activity and gene expression

Heparin-releasable LPL activity, expressed per gram of adipose tissue, was significantly lower in diabetic subjects both at fasting and after the meal compared with the other 2 groups (Table 2).

3.8. Correlation analyses

In the 3 groups combined, fasting plasma adiponectin was correlated with HDL cholesterol ($r = 0.76$, $P < .001$) and heparin-releasable LPL activity in adipose tissue ($r = 0.68$, $P < .001$) (Fig. 3). Six hours postmeal, plasma adiponectin levels were correlated inversely with total plasma triglyceride and with chylomicron triglyceride and cholesterol concentrations, and directly with HDL cholesterol and heparin-releasable LPL activity in adipose tissue ($P < .05$ for all) (Fig. 3).

4. Discussion

This study shows that adiponectin levels are acutely regulated by a fat-rich meal. This regulation, which concerns both plasma levels of adiponectin and its gene expression in

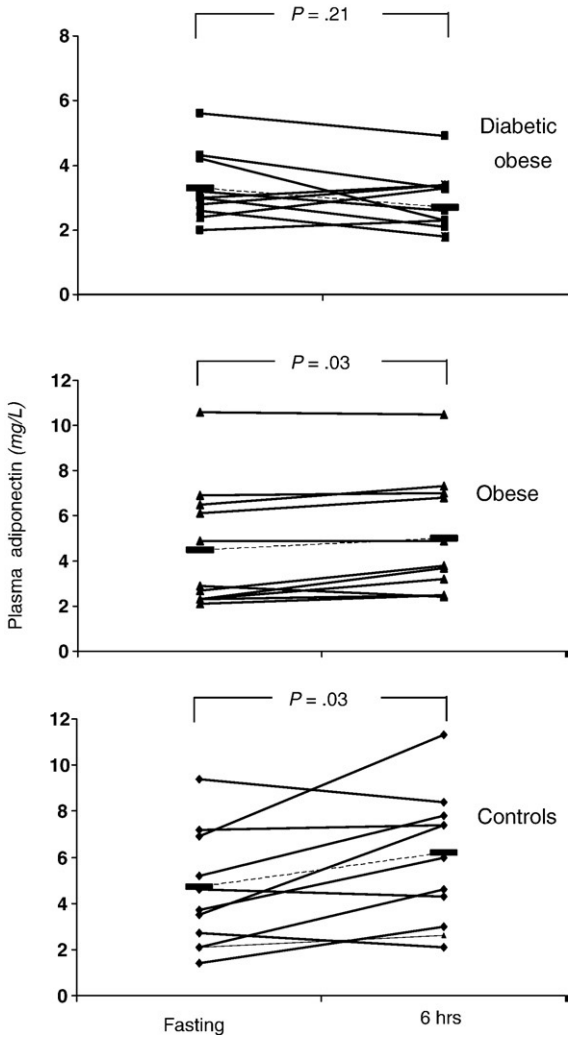

Fig. 1. Individual and mean adiponectin plasma concentrations before and 6 hours after a standard meal in obese subjects with diabetes (squares) and without diabetes (triangles) and in normal-weight controls (lozenges).

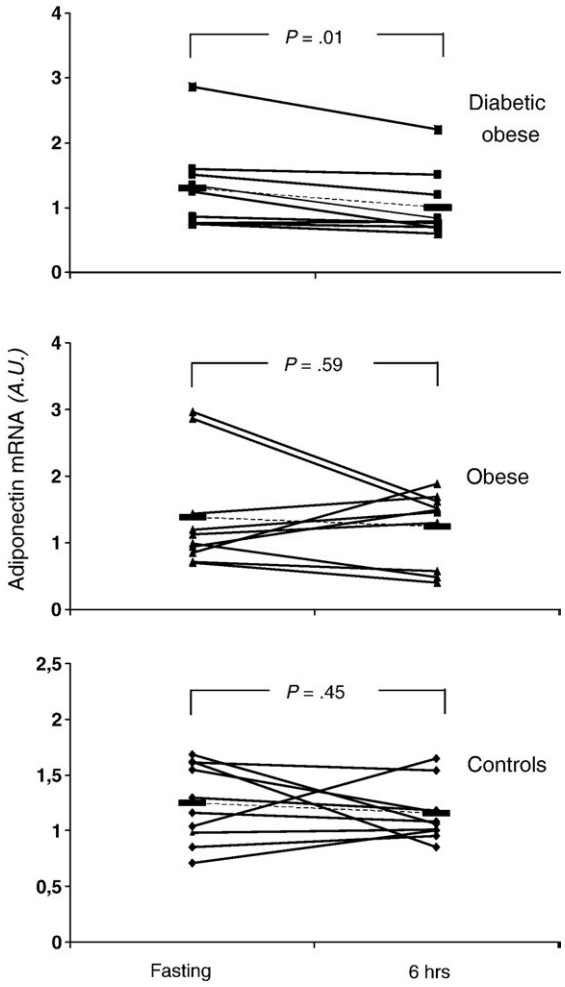

Fig. 2. Individual and mean adiponectin adipose tissue mRNA before and 6 hours after a standard meal in obese subjects with diabetes (squares) and without diabetes (trianges) and in normal-weight controls (lozenges).

adipose tissue, is different according to the metabolic status of an individual. In fact, patients with type 2 diabetes mellitus show a postprandial decrease in adiponectin, which significantly differs from postprandial changes in either obese or normal-weight nondiabetic individuals. This finding is relevant because it demonstrates that the differences in adiponectin levels observed in diabetic patients and linked to metabolic and cardiovascular effects are also dependent on everyday operating nutritional factors, which are expected to be small and, therefore, difficult to detect. Moreover, acute adiponectin changes were independent of differences in body fat content because diabetic subjects were matched with equally obese ones.

Fasting adiponectin levels were not significantly different between nondiabetic obese and normal-weight subjects. Although it cannot be ruled out that this was due to the relatively small sample size, the adiposity and whole-body insulin sensitivity indices, similarly altered in the obese and the diabetic groups, would indicate that our nondiabetic obese subjects—with normal oral glucose tolerance and fasting lipid levels—had impaired muscle glucose metabolism but preserved insulin sensitivity in relation to adiponectin metabolism in adipose tissue and/or liver. This is in line with the observation that obese subjects without the metabolic syndrome had serum adiponectin concentrations similar to those in the normal-weight reference group [22].

Previous results on postprandial adiponectin changes have been very controversial [10-12,23]. Different meal compositions may contribute to explain these inconsistencies, adiponectin changes being observed more often with a very high fat content of the meal [24,25]. In fact, a decrease in adiponectin level was induced by a high-fat and not by a high-carbohydrate meal [25]. In addition, in not acute studies, the intake of certain fatty acids differentially affected serum adiponectin levels in mice and adiponectin gene expression in mouse WAT and 3T3-L1 adipocytes, the effects being time dependent and depot specific [26]. Moreover, the glycemic index/fiber content of the meals could influence adiponectin levels [25,27]. Another explanation could be sex, which is known to considerably affect adiponectin levels. In this respect, in our study as in the study by Musso et al [24], postprandial changes have been observed in men. In addition, in these 2 studies, a longer observation time after meal (6 hours) was necessary to detect adiponectin changes.

In our study, the differences between the groups are strengthened by the fact that adiponectin changes were observed in both plasma and adipose tissue gene expression; as a matter of fact, this is the first study that shows

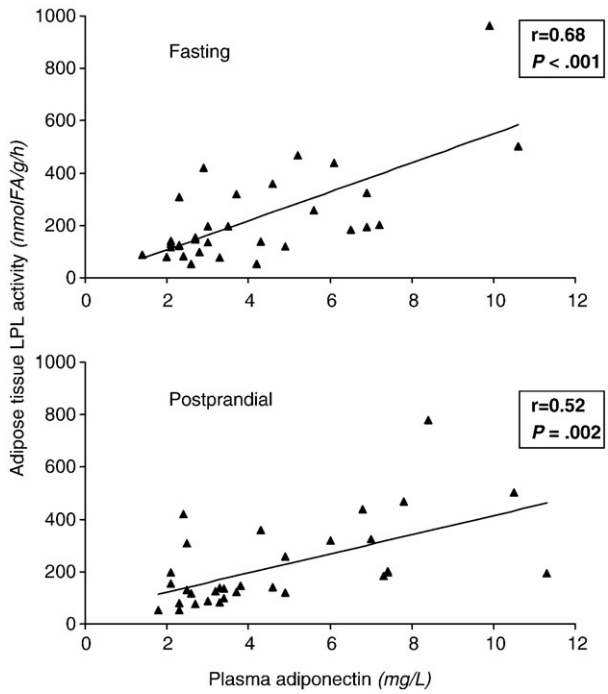

Fig. 3. Relationship between plasma adiponectin levels and adipose tissue LPL activity in the fasting condition (upper) and 6 hours after meal (lower) in all subjects participating in the study.

postprandial changes in adiponectin gene expression. Our data indicate that the postprandial differences observed between the groups seem to originate at the transcription level because adiponectin mRNA was significantly decreased after the meal in diabetic subjects but not in the other 2 groups. This matches the absence of postprandial changes in adiponectin plasma levels in diabetic subjects vs the significant increases in the obese and control groups. These positive postprandial changes in plasma levels compared with the changes in gene expression imply the effect of additive posttranslational factor(s) equally operating in all groups and modulating postprandial plasma adiponectin levels independently of metabolic status. An argument in favor of the hypothesis that other factors in addition to gene expression are important determinants of serum adiponectin levels is provided by the absence of a statistically significant correlation between plasma concentrations and adipose tissue mRNA levels of adiponectin, which is in line with previous findings [22]. It is possible that in the postprandial condition the increase in plasma adiponectin levels is due to an impairment in hepatic adiponectin clearance consistent with biliary changes after a fat-rich meal ingestion [28], as well as to a delayed renal clearance consistent with a postprandial reduction in glomerular filtration rate [29].

Which mechanisms underlie the different postprandial adiponectin response in the diabetic group? Insulin resistance has been suggested to play a role in inducing a lower plasma adiponectin response to an oral fat load in patients with nonalcoholic steatohepatitis compared with healthy controls [24]. We did not observe any major effect of insulin resistance on adiponectin because obese subjects with and without diabetes differed for adiponectin response, but not for insulin sensitivity at the muscle level (insulin-stimulated glucose disposal). As discussed above, this does not exclude the possibility of an impaired insulin sensitivity at the level of adipose tissue and/or liver in diabetic subjects, particularly in relation to adiponectin metabolism, which would be in line with the evidences that adiponectin correlates more with insulin sensitivity than with body mass [30].

Another explanation for the different postprandial adiponectin response in diabetic and nondiabetic individuals could be differences in postprandial insulin levels. In this respect, in our study, the late insulin response to the meal was similar in the 2 obese groups. However, we did not measure the early postprandial insulin response that is, nevertheless, known to be impaired in individuals with type 2 diabetes mellitus. It is therefore possible that in normoglycemic individuals the early postprandial insulin secretion induces an adiponectin increase that is not observed in diabetic patients in whom the early insulin secretion is grossly impaired.

Anyhow, the relation between insulin and adiponectin remains rather controversial, particularly concerning how—or if—they regulate each other. Insulin has been shown to increase adiponectin secretion [31,32]; and in another study, it induced an almost 2-fold rise in adiponectin gene expression in cultured human adipocytes [33]. Moreover, Pereira and Draznin [34] showed that insulin increased adiponectin secretion, without increasing adiponectin mRNA. Furthermore, in patients with severe insulin resistance (due to insulin receptor defects), very high insulin levels are associated with extremely high adiponectin levels [35,36]. In contrast with these observations, in an in vitro model, insulin induced a decrease in adiponectin gene expression [37]. Moreover, no significant association between the changes in serum adiponectin and the changes in insulin was observed in obese subjects with and without the metabolic syndrome before, during, and after diet-induced weight reduction [22]. Similarly, in acute studies, no correlations were found between postmeal changes in adiponectin and insulin plasma levels [25].

In our population, adiponectin changes after the meal were inversely correlated with changes in triglyceride-rich lipoproteins. This correlation has also been shown in individuals with nonalcoholic steatohepatitis after a meal composed of fat only and, therefore, not inducing postprandial changes in insulin levels [24]. The association between postprandial lipids and adiponectin could be explained by changes in the main lipolytic enzyme (ie, LPL). An association between adiponectin and postheparin plasma LPL activity has already been reported [16]. Our study shows for the first time that the association refers to the LPL activity in adipose tissue. An association between adiponectin and accelerated postprandial lipolytic cascade is in line with the strong correlation observed in our study between adiponectin and HDL cholesterol levels, which reproduces a finding that has been consistently reported before [38]. A role in this relationship could be played by hepatic lipase activity [39], which is increased in individuals with type 2 diabetes mellitus also in the postprandial state [14,15].

There are some limitations to the possibility of generalizing our results to the entire diabetic population. First, we studied a male population; and we do not know if these results also apply to women, who have higher levels of plasma adiponectin and, therefore, a likely different regulation. Second, our group of diabetic obese individuals was rather healthy as compared with most diabetic patients; and this may have induced an underestimation of the true association, likely more marked in the whole diabetic population. Finally, we have no information on adiponectin subtypes (high– and low–molecular weight adiponectin), which may show different patterns than the total adiponectin level.

In conclusion, type 2 diabetes mellitus is associated with lower postprandial plasma levels and adipose tissue gene expression of adiponectin. The abnormal adiponectin response is independent of degree of adiposity and whole-body insulin resistance, suggesting a deleterious regulation induced by feeding specifically in diabetic patients, possibly due to their reduced early postprandial

insulin response. The reduced adiponectin could impair postprandial lipoprotein metabolism.

Further investigation is warranted considering the potential pathogenic relevance of adiponectin and the fact that changes in its postprandial response are elicited by stimuli, like feeding, which are very frequent in the everyday life. In particular, it is worth to further evaluate whether foods rich in fat, protein, or carbohydrate influence this process differently in patients with various degrees of impairment in blood glucose metabolism.

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