High Adiponectin Concentrations Are Associated with the Metabolically Healthy Obese Phenotype

Carlos A. Aguilar-Salinas, Eduardo García García, Lorena Robles, Daniela Riaño, Doris Georgina Ruiz-Gomez, Ana Cristina García-Ulloa, Marco A. Melgarejo, Margarita Zamora, Luz E. Guillen-Pineda, Roopa Mehta, Samuel Canizales-Quinteros, Ma Teresa Tusie Luna, and Francisco J. Gómez-Pérez

Departamento de Endocrinología y Metabolismo del Instituto Nacional de Ciencias Médicas y Nutrición "Salvador Zubirán" (C.A.A.-S., L.R., D.R., A.C.G.-U., M.A.M., L.E.G.-P., R.M., F.J.G.-P.), 14000 México D.F., Mexico; Departamento de Obesidad del Instituto Nacional de Ciencias Médicas y Nutrición "Salvador Zubirán" (E.G.G., D.G.R.-G., M.Z.), 14000 México D.F., Mexico; and Unidad de Biología Molecular y Medicina Genómica, Instituto Nacional de Ciencias Médicas y Nutrición (S.C.-Q., M.T.T.L.), Instituto de Investigaciones Biomédicas de la Universidad Nacional Autónoma de México, 14000 México D.F., México

Context: In the *ob*/*ob* mice, keeping adiponectin concentrations in the physiological range (through overexpression of this gene in the adipose tissue) results in expansion of fat mass and protection against metabolic co-morbidities.

Objective: The aim of the study was to test in humans whether plasma adiponectin levels, similar to those found in lean subjects, are associated with the metabolically healthy obese phenotype.

Design and Setting: A cross-sectional analysis was performed of a cohort of obese and nonobese subjects aged 18–70 yr. A medical history was taken, and glucose, plasma lipids, and total adiponectin were measured.

Participants: We studied 189 men and 527 women. The majority were obese (n = 470, 65.6%). The metabolically healthy obese phenotype was found in 38 men and 133 women. This is defined as a body mass index (BMI) above 30 kg/m^2 plus high-density lipoprotein cholesterol of at least 40 mg/dl in the absence of type 2 diabetes and arterial hypertension.

Results: Twenty percent of the cases with a BMI above 40 kg/m^2 had adiponectin concentrations above the median value of normal BMI subjects. Adiponectin levels above 12.49 mg/liter in obese women (odds ratio, 3.02; 95% confidence interval, 1.95–4.67; $P < 0.001$) and above 8.07 mg/liter in obese men (odds ratio, 2.14; 95% confidence interval, 1.1–4.06; $P = 0.01$) increased the probability of being metabolically healthy. The association remained significant (β, 0.673 $\pm$ 0.205, $P < 0.001$) in a logistic regression model ($r^2 = 0.25$, $P < 0.001$) after controlling for the confounding effect of age, insulin, and waist circumference.

Conclusions: Certain obese individuals have adiponectin levels similar to those found in normal BMI subjects; this is associated with the metabolically healthy obese phenotype. **(*J Clin Endocrinol Metab* 93: 4075–4079, 2008)**

Some obese individuals (especially in the class III obesity range) are free of metabolic complications although their clinical characteristics are no different from those of obese individuals with obesity-related comorbidities. This condition has been named the "metabolically healthy obese phenotype" (1–4). Possible explanations for the protection against metabolic abnormalities remain to be identified.

The description of the role of adiponectin in the pathophysiology of obesity is an ongoing process (5, 6). Early in the study of adiponectin, an inverse relationship between body mass index

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Abbreviations: BMI, Body mass index; HDL, high-density lipoprotein; HMW, high molecular weight.

(BMI) and adiponectin concentrations was confirmed both in humans and in animal models (7–12). However, recent experimental studies have reported that overexpression of the adiponectin gene in the adipose tissue of the *ob*/*ob* mouse increased plasma adiponectin concentrations, keeping them in a physiological range; this change led to a remarkable weight gain and amelioration of hyperglycemia and metabolic abnormalities (13). Based on this observation, we propose that variations in plasma adiponectin concentration may be a potential player in the pathophysiology of the metabolically healthy obese phenotype. Our data show that the lack of suppression of adiponectin concentrations is independently associated with the metabolically healthy obese phenotype.

Subjects and Methods

Study population

Subjects aged 18–70 yr were recruited from the obesity and lipid disorders clinics of the Instituto Nacional de Ciencias Médicas y Nutrición from June 2006 to June 2007. Patients were invited to participate at their initial visit or if they had quit lipid-lowering therapy (for reasons nonrelated to the study) for more than 6 wk. Healthy volunteers were also invited to participate. These were detected among unaffected relatives of patients that attend these clinics. To avoid confounding factors known to affect plasma lipid and glucose levels, the following exclusion criteria were applied: any smoking during the previous 6 months; subjects with cardiac arrhythmia, congestive heart failure, recent stroke, chronic renal disease, macroalbuminuria (expressed as albumin/creatinine ratio >300 μg/mg), or severe dyslipidemia [triglycerides >600 mg/dl (6.74 mmol/liter) or cholesterol >300 mg/dl (7.89 mmol/liter)]; any severe chronic disease; or any acute or chronic inflammatory illness. Subjects were also excluded if they were on medications with known effects on lipoprotein metabolism, except for metformin, angiotensin receptor blockers, and angiotensin-converting enzyme inhibitors, which were allowed therapies. The Ethics Committee approved the protocol, and all participants gave written informed consent.

Study protocol

Patients visited the clinic after a 9- to 12-h fasting period. A standardized questionnaire was administered to all participants. Demographic data and information about comorbid conditions and the use of medication, tobacco, and alcohol was obtained. Height, weight, waist circumference, and blood pressure were measured in all cases. Blood samples were collected after a 12-h fasting period. All assays were conducted at the Department of Endocrinology and Metabolism laboratory. This laboratory is certified for standardization of the tests by the External Comparative Evaluation of Laboratories Program of the College of American Pathologists. Glucose, total cholesterol, high-density lipoprotein (HDL)-cholesterol, triglycerides, liver function tests, and creatinine were measured using the Synchron CX analyzer (Beckman Systems, Fullerton, CA). The coefficients of variation for cholesterol and HDL cholesterol are 3.3 and 2.5%, respectively. LDL cholesterol concentration was estimated by the Friedewald formula. Plasma insulin concentrations were estimated using a RIA method. High sensitivity C-reactive protein was measured in plasma in duplicate using an ELISA method (Dade Behring, Deerfield, IL). Total adiponectin was measured using an ELISA method (Linco, St. Louis, MO). Leptin concentration was measured using an ELISA method (Linco, St. Louis, MO).

TABLE 1. Characteristics of the metabolically healthy obese subjects (MHO) and their controls

BMI strata (kg/m^2)	Age (yr)	Gender (M/F)	Adiponectin (mg/liter)	Waist (cm)	Triglycerides (mg/dl)	HDL cholesterol (mg/dl)	Insulin (mU/liter)	Leptin (mg/liter)
15–19.9 Total (n = 37)	25.6 ± 5.4	5/32	12.5 ± 4.4	69.6 ± 7	87 ± 27	52.2 ± 11	7.1 ± 3	7.2 ± 4
Metabolically healthy (n = 31)	25.6 ± 5.8	3/28	13.2 ± 0.8	69.1 ± 1.2	89 ± 5.5	55.1 ± 1.8	6.5 ± 0.5	7.4 ± 1.2
Metabolically unhealthy (n = 6)	25.8 ± 3.0	2/4	9.0 ± 1.9[a]	71.8 ± 2	79 ± 13	36.6 ± 4.3[a]	9.9 ± 1.2[a]	3.7 ± 4.1
20–24.9 Total (n = 136)	34.1 ± 13.0	37/99	11.6 ± 4.4	79.2 ± 7	115.4 ± 80	51.0 ± 12	9.2 ± 12	10.8 ± 8
Metabolically healthy (n = 106)	31.6 ± 11.2	21/85	12 ± 0.4	80.1 ± 0.5	108 ± 13	54.5 ± 0.8	8.8 ± 1	10.9 ± 1.1
Metabolically unhealthy (n = 30)	42.9 ± 15.4	16/14	10.4 ± 0.8[a]	80.9 ± 0.9	221 ± 23[a]	39.2 ± 1.5[a]	10.7 ± 1.7	10 ± 2.4
25–29.9 Total (n = 73)	48.1 ± 13.7	27/46	10.4 ± 4.4	92.4 ± 9	249 ± 206	43.3 ± 9	14.2 ± 9	27.1 ± 11
Metabolically healthy (n = 34)	47.0 ± 13.9	5/29	11.2 ± 0.6	90.6 ± 1	179 ± 24	49.1 ± 1.1	11.7 ± 1.6	25.4 ± 3.9
Metabolically unhealthy (n = 39)	49.3 ± 13.4	22/17	9.3 ± 0.7[a]	92.2 ± 0.9[a]	306 ± 22[a]	37.2 ± 1[a]	14.5 ± 0.9[a]	30.5 ± 5.6
30–34.9 Total (n = 177)	43.1 ± 13.5	60/117	9.3 ± 3.9	101.2 ± 9	232.7 ± 220	43.2 ± 10	14.1 ± 9	27.3 ± 17
MHO (n = 84)	41.1 ± 13.4	30/54	10.5 ± 0.4	99.7 ± 0.8	171 ± 89	49 ± 0.8	12.4 ± 1.1	29.6 ± 2.1
NoMHO (n = 93)	44.8 ± 13.3	30/63	8.0 ± 0.3[a]	102.3 ± 0.7[a]	290 ± 19[a]	37.3 ± 0.7[a]	16.2 ± 0.9[a]	24.5 ± 2.0[a]
35–39.9 Total (n = 127)	44.1 ± 12.6	24/103	9.2 ± 3.4	113.8 ± 11	208 ± 131	42.6 ± 10	19.3 ± 15	42.9 ± 20
MHO (n = 40)	44.8 ± 11.9	4/36	9.9 ± 0.5	111.7 ± 1.7	161 ± 20	49.3 ± 1.4	17.2 ± 2.4	44.1 ± 5.8
NoMHO (n = 87)	43.7 ± 12.8	20/67	8.8 ± 0.3[a]	114.3 ± 1.1[a]	233 ± 13[a]	38.9 ± 0.9[a]	20.1 ± 1.6[a]	42.3 ± 2.5
≥40 Total (n = 166)	39.1 ± 11.5	36/130	9.9 ± 4.2	130.4 ± 16	184 ± 88	40.4 ± 9	24.0 ± 14	55.7 ± 23
MHO (n = 47)	37.5 ± 11.5	4/43	9.8 ± 0.5	127.3 ± 2.3	158 ± 12	49.4 ± 1	21.8 ± 2	62.5 ± 4.1
NoMHO (n = 119)	39.7 ± 11.5	32/87	9.0 ± 0.3[a]	131.5 ± 1.3[a]	190 ± 7[a]	37.2 ± 0.6[a]	24.8 ± 1.3[a]	53.3 ± 2.3[a]

MHO represents metabolically healthy obese subjects defined as a BMI above 30 kg/m^2 in conjunction with HDL cholesterol of at least 40 mg/dl and the absence of type 2 diabetes and arterial hypertension. Besides the obese individuals, each BMI strata was divided based on the absence (metabolically healthy) or the presence (metabolically unhealthy) of one or more of the following metabolic abnormalities: HDL cholesterol ≥40 mg/dl, type 2 diabetes, and arterial hypertension. Data are presented as mean ± SD for each BMI strata. Data for BMI substrata are adjusted for age and gender. NoMHO, Not metabolically healthy obese.

[a] $P < 0.05$ against the BMI-corresponding metabolically healthy subjects adjusted for age and gender.

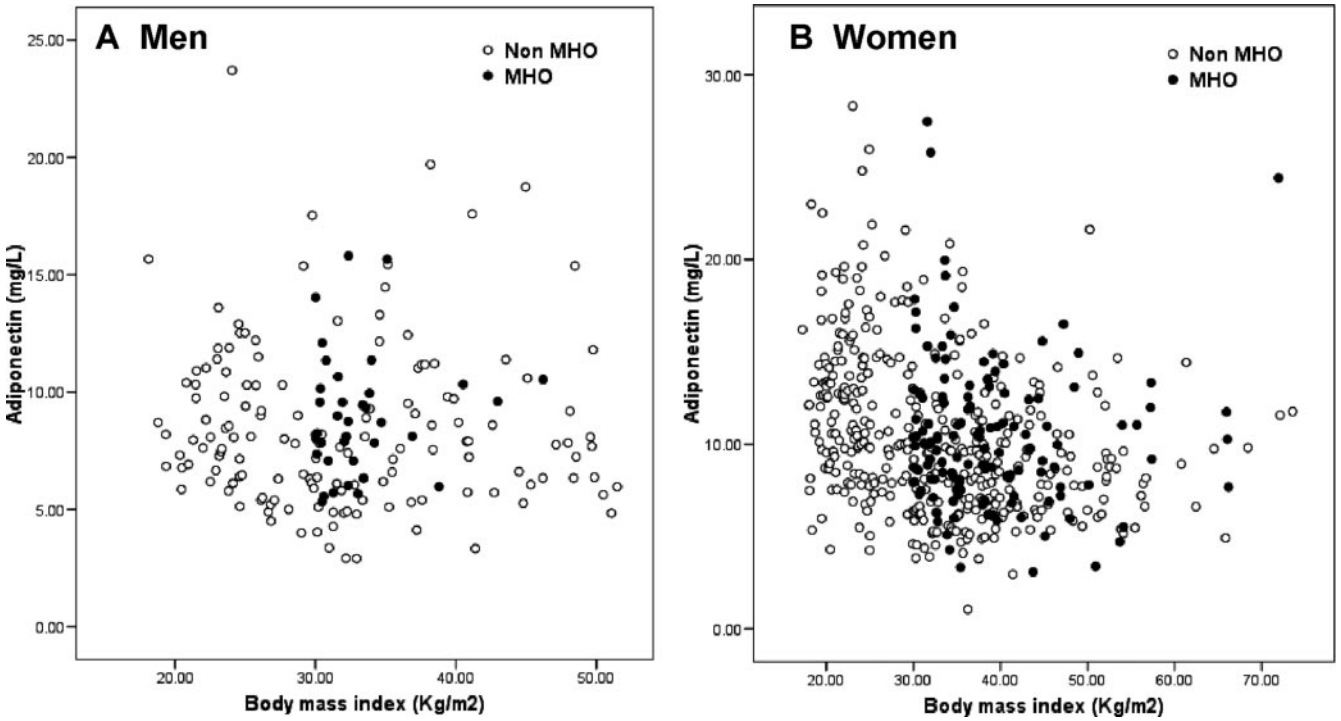

FIG. 1. The distribution of plasma adiponectin concentrations in cases with or without the metabolically healthy obese phenotype (MHO). There are a significant number of obese individuals that have adiponectin concentrations in the same range as that observed in lean subjects (median value for lean men, 8.07 mg/liter; and for lean women, 12.49 mg/liter). Subjects with the metabolically healthy obese phenotype are identified using *filled dots*. Data are stratified by gender (A, men; B, women).

Definitions

Class III obesity is defined as a BMI of at least 40 kg/m^2 (14). Type 2 diabetes was considered present in subjects with a random glucose concentration of at least 200 mg/dl, a fasting glucose of at least 126 mg/dl, a 2-h post challenge glucose value of at least 200 mg/dl, or those receiving glucose-lowering medication. Arterial hypertension was defined as the use of antihypertensive treatment and/or a blood pressure above normal (>140 mm Hg systolic and/or >90 mm Hg diastolic). The metabolically healthy obese phenotype is defined as the presence of a BMI above 30 kg/m^2 in conjunction with a HDL cholesterol level of at least 40 mg/dl and the absence of type 2 diabetes and arterial hypertension.

Statistical analysis

This was performed using SPSS for Windows, version 15. Analysis of covariance tests (using age and gender as covariates) were used for assessing differences between groups for continuous variables. All categorical variables were analyzed using the χ^2 test. Stepwise logistic regression models were constructed to assess the association between the metabolically healthy obese phenotype and adiponectin concentrations.

Results

Characteristics of the study population

The study included 716 patients (189 men and 527 women). The mean age was 41 ± 12 yr, and the mean BMI was 33.9 ± 10 kg/m^2. Their characteristics are shown in Table 1, where subjects are stratified according to BMI. The majority of the population was obese (n = 470, 65.6%). Class III obesity was present in 166 individuals (23.2% of the population).

The metabolically healthy obese phenotype was found in 171 cases (67 men and 104 women). The prevalence of this phenotype by BMI strata is shown in Table 1. Almost one third of the class III obese individuals (n = 47, 28.3%) were free of metabolic abnormalities. Metabolically healthy obese cases had the same age, gender, and plasma leptin concentrations as their obese peers, but their waist circumference was significantly smaller (117 ± 17 *vs.* 110 ± 16 cm; $P < 0.001$).

Adiponectin and the "metabolically healthy obese" phenotype

The distribution of the plasma adiponectin concentrations of patients with or without the metabolically healthy obese phenotype is shown in Fig. 1. Data for men and women are shown separately. In accordance with our hypothesis, there are a significant number of obese individuals that have adiponectin concentrations in the same range as that observed in lean subjects. The dispersal of the adiponectin concentration increased as BMI rose above 40 kg/m^2. The metabolically healthy obese cases were more frequently found among those with the higher adiponectin concentrations.

We analyzed the characteristics of the obese cases that had "higher than expected" adiponectin concentrations. The "normal" ranges for plasma adiponectin vary between publications (9, 12); as a result, we selected as a threshold an adiponectin concentration most likely to be associated with a healthy profile. The median value found in men (8.07 mg/liter) and women (12.49 mg/liter) with a BMI between 20 and 24.9 kg/m^2 was used for this purpose. The percentage of cases that had an adiponectin level above these cutoff points had an inverse relationship with the BMI (Table 2). Almost 20% of the class III obese cases (n = 34, 20.5%) fulfilled this criteria. These patients had significantly lower plasma glucose ($P <$

TABLE 2. Characteristics of the participants stratified by their adiponectin concentration (above or below the median value found in the cases with BMI 20–24.9 kg/m^2)

BMI strata (kg/m^2)	Age (yr)	Gender (M/F)	Adiponectin (mg/liter)	Waist (cm)	Triglyceride (mg/dl)	HDL cholesterol (mg/dl)	Insulin (mU/liter)	Leptin (mg/liter)
15–19.9 (n = 37)								
Adip<p50, n = 19 (51.4%)	26.4 ± 5	3/28	9.2 ± 0.85	68.4 ± 1.1	79 ± 8	45.9 ± 2.7	7.1 ± 0.6	5.8 ± 1.8
Adip>p50, n = 18 (48.6%)	24.9 ± 6	2/4	15.8 ± 0.9[a]	69.7 ± 1.2	86 ± 8	61.0 ± 2.8[a]	5.8 ± 0.6	8.5 ± 1.8
20–24.9 (n = 136)								
Adip<p50, n = 68 (50%)	33.9 ± 12	19/49	8.6 ± 0.3	80 ± 0.8	137 ± 9.9	47.8 ± 1.3	10.2 ± 1.8	11.9 ± 1.3
Adip>p50, n = 68 (50%)	37.2 ± 14	18/50	15 ± 0.4[a]	77 ± 0.9	95 ± 10[a]	53.1 ± 1.3[a]	8.8 ± 1.9	9.3 ± 1.4
25–29.9 (n = 73)								
Adip<p50, n = 47 (64.4%)	4780 ± 13	17/30	7.8 ± 0.3	93 ± 1.1	291 ± 28	41.2 ± 1.2	16.5 ± 1.2	25.2 ± 4.2
Adip>p50, n = 26(35.6%)	49.8 ± 14	10/16	14.9 ± 0.4[a]	91 ± 1.6	181 ± 38[a]	46.9 ± 1.6[a]	9.9 ± 1.6[a]	30.1 ± 5.3
30–34.9 (n = 177)								
Adip<p50, n = 132 (74.6%)	43.1 ± 13	40/92	7.5 ± 0.2	101 ± 0.7	267 ± 20	40.6 ± 0.7	14.5 ± 0.7	24.9 ± 1.7
Adip>p50, n = 45 (25.4%)	43.9 ± 13	20/25	14.1 ± 0.3[a]	99.8 ± 1.3	158 ± 34[a]	48.5 ± 1.2[a]	13.0 ± 1.5	34.2 ± 2.8[a]
35–39.9 (n = 127)								
Adip<p50, n = 97 (76.4%)	42.4 ± 12	12/85	7.6 ± 0.2	114 ± 1.1	211 ± 14.1	40.6 ± 1.1	21.1 ± 1.7	40.5 ± 2.4
Adip>p50, n = 30 (23.6%)	47.4 ± 13	12/18	14.1 ± 0.4[a]	112 ± 2.1	184 ± 25	48.7 ± 1.8[a]	14.7 ± 3[a]	49.7 ± 4.3[a]
≥40 (n = 166)								
Adip<p50, n = 131 (78.9%)	37.4 ± 10	24/107	7.9 ± 0.2	132 ± 1.4	185 ± 7.9	39.3 ± 0.7	25.8 ± 1.2	55.8 ± 2.3
Adip>p50, n = 35 (21.1%)	45.3 ± 13	12/23	14.6 ± 0.5[a]	126 ± 0.2[a]	177 ± 15	44.0 ± 1.5[a]	15.8 ± 2.4[a]	55.4 ± 4.6

Data are adjusted for age and gender. Adip>p50 or Adip<p50, Adiponectin concentrations above or below the median value found in men (8.07 mg/liter) and women (12.49 mg/liter) with a BMI between 20 and 24.9 kg/m^2.

[a] $P < 0.05$ against the BMI-corresponding cases with adip<p50 adjusted for age and gender.

0.001), triglycerides ($P < 0.001$), insulin ($P < 0.001$), and C-reactive protein concentrations compared with their peers with the same BMI. Also, they had higher HDL cholesterol concentrations ($P < 0.001$) (Table 2). The prevalence of the metabolically healthy obese was significantly higher among obese cases with adiponectin levels above the median value found in lean subjects compared with the remaining cases (47.6 *vs.* 32%; $P = 0.003$). This finding had a strong statistical significance among women ($P = 0.004$), but it was borderline among men ($P = 0.05$) due probably to a smaller sample size. These results suggest that the plasma adiponectin concentrations have a protective effect against obesity-related metabolic derangements. To confirm the clinical impact of the "higher than expected" adiponectin concentrations, we evaluated whether these levels were associated with the metabolically healthy obese phenotype. Indeed, an adiponectin concentration above 12.49 mg/liter in obese women significantly increased the probability for being metabolically healthy (odds ratio, 3.02; 95% confidence interval, 1.95–4.67; $P < 0.001$). The same phenomenon was observed in men with an adiponectin concentration above 8.07 mg/liter (odds ratio, 2.14; 95% confidence interval, 1.1–4.06; $P = 0.01$). The association remained significant (β, 0.673 ± 0.205, $P < 0.001$) in a logistic regression model ($r^2 = 0.25$, $P < 0.001$) after controlling for the confounding effect of age (β, −0.026 ± 0.007, $P < 0.001$), insulin (β, −0.018 ± 0.005, $P = 0.043$), and waist circumference (β, −0.034 ± 0.005, $P < 0.001$).

Discussion

Kim *et al.* (13) have shown that the expansion of adipose tissue induced by the adipose tissue-specific overexpression of the adiponectin gene results in decreased ectopic lipid deposition and a significant improvement in obesity-associated complications in *ob/ob* mice. Our objective was to explore whether a similar scenario occurs naturally in humans. We analyzed the plasma adiponectin concentrations and other metabolic variables in 716 patients, of which 166 were class III obese. A subset of obese individuals has higher plasma adiponectin concentrations than the median level found in lean healthy subjects, and these individuals have minor or no metabolic abnormalities. Indeed, 20.5% of all class III obese cases had higher adiponectin concentrations; these individuals had lower plasma glucose, triglycerides, insulin, and C-reactive protein and higher HDL cholesterol concentrations compared with their peers with the same BMI. Adiponectin levels above the median value found in lean subjects increased the probability of being metabolically healthy. This association remained significant after adjusting for the presence of confounding variables. Thus, our results extend the available information, linking the lack of repression of adiponectin concentrations with protection against metabolic disturbances in obese subjects.

The metabolically healthy obese phenotype has been identified by several groups (15, 16); usually, such cases are less insulin resistant and have a smaller waist circumference compared with the control peers. As yet, no potential mechanism has been postulated to explain the relative protection from obesity-related metabolic complications enjoyed by these individuals. This report supplements the available information by showing that higher than expected adiponectin concentrations are independently associated with this phenotype. Additional studies are required to identify reasons for this association. If we consider that a substantial proportion (30–70%) of the variability in plasma adiponectin levels is accounted for by genetic factors, variation in the adiponectin gene is a plausible explanation (17,

18). For example, SNPg.-11391G→A and other less frequent variants (*i.e.* G84R, G90S, I164T, and R112C) are associated with variations in plasma adiponectin concentrations. However, the relationship with the metabolically healthy obese phenotype has not been studied, and there are controversial results regarding the contribution of these alleles to variations in metabolic traits. Furthermore, some adiponectin encoding gene variants are associated with severe forms of obesity. This has been reported by Bouatia-Naji *et al*. for the promoter SNPs −11,377C and +276T (19). The allele −11,377C was associated with lower fasting insulin in obese children; despite this, the difference was not related to differences in plasma adiponectin concentrations. Variations in other genes that influence adiponectin synthesis (*i.e.* PPAR-γ) or action (adiponectin receptors) should also be explored.

There is very limited information about adiponectin concentrations in severely obese cases. Our report is not the first to find higher than expected adiponectin concentration in class III obesity. Vendrel *et al*. (20) found higher adiponectin levels in 57 class III obese cases compared with 117 class I-II obese individuals. However, they did not find an association between insulin sensitivity and adiponectin levels. The authors did not make a separate analysis based on the presence of metabolic abnormalities.

The limitations of our report are the measurement of total adiponectin [instead of the high molecular weight (HMW) form], the absence of genetic data, the cross-sectional design of the study, and a moderate sample size. HMW adiponectin is more strongly associated with markers of insulin sensitivity than total adiponectin (21). HMW adiponectin is the fraction responsible for the adiponectin-induced suppression of the hepatic glucose production and the inhibition of endothelial cell apoptosis. Despite this finding, we were able to identify an association between adiponectin and the metabolically healthy obese phenotype. It is likely that this association will be even stronger on measurement of HMW adiponectin. We recognize that the number of cases included in some BMI strata is small (Table 1) and our population is composed mainly by women. However, we do have a large number of cases with a BMI of at least 30 kg/m^2 (n = 460), enabling us to include a sufficient number of metabolically healthy obese individuals. On the other hand, the association between adiponectin and the metabolically healthy obese phenotype was found mainly in women, but it has a borderline statistical significance in men as well. Also, the percentage of obese cases with higher than expected adiponectin concentrations may be different in other clinical settings due to referral bias. Finally, we recognize that the definition of the metabolically healthy obese status used in this study could be considered arbitrary.

In summary, certain obese individuals have adiponectin concentrations similar to those found in normal body weight subjects. This characteristic is independently associated with the metabolically healthy obese phenotype. Additional studies will be required to test this hypothesis in a mechanistic fashion.

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Address all correspondence and requests for reprints to: Carlos Alberto Aguilar-Salinas, Departamento de Endocrinología y Metabolismo del Instituto Nacional de Ciencias Médicas y Nutrición "Salvador Zubirán," Vasco de Quiroga 15, Mexico D.F. 14000, México. E-mail: caguilarsalinas@yahoo.com.

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