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Adipose Tissue Adiponectin Production and Adiponectin Serum Concentration in Human Obesity and Insulin Resistance

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The role of adiponectin production for the circulating protein concentration in human obesity and insulin resistance is unclear. We measured serum concentration and sc adipose tissue secretion rate of adiponectin in 77 obese and 23 nonobese women with a varying degree of insulin sensitivity. The serum adiponectin concentration was similar in both groups. In obesity, adiponectin adipose tissue secretion rate per weight unit was reduced by 30% ($P = 0.01$), whereas total body fat secretion rate was increased by 100% ($P < 0.0001$). In the group being most insulin resistant (1/3), serum concentration ($P < 0.001$) and adipose tissue secretion rate per tissue weight ($P < 0.05$) were reduced, whereas total body fat secretion rate was increased ($P < 0.01$), by about 30%. The adipose tissue secretion rate of adiponectin was related to the serum concentration ($P = 0.005$) but explained only about 10% of the interindividual variation in circulating adiponectin and insulin sensitivity. The plasma adiponectin half life was long, 2.5 h. In conclusion, the role of protein secretion for the circulating concentration of adiponectin and insulin sensitivity under these conditions is minor because adiponectin turnover rate is slow. Although increased in obesity and insulin resistance, total body production of adiponectin is insufficient to raise the circulating concentration, may be due to reduced secretion rate per tissue unit. (*J Clin Endocrinol Metab* 89: 1391–1396, 2004)

ADIPOSE TISSUE SECRETES several proteins that have various autocrine/paracrine or endocrine functions, including body weight regulation and glucose/lipid homeostasis. One protein is adiponectin, which is produced exclusively in adipose tissue and circulates in blood at high concentrations (1, 2). Studies in rodents suggest a role for adiponectin in insulin resistance. When injected, adiponectin accelerates the oxidation of nonesterified fatty acids, which is accompanied by decreased plasma levels of glucose (3). Long-term (12-d) administration of adiponectin decreases triglyceride storage in liver and muscle, improves hyperglycemia, and decreases plasma triglyceride and free fatty acid concentrations (4). In mouse hepatocytes, adiponectin improves the suppression of gluconeogenesis by insulin (5). Moreover, adiponectin-deficient mice show insulin resistance and neointimal formation (6). Two putative receptors for adiponectin have recently been detected; one is predominantly expressed in skeletal muscle, and the other one is expressed mainly in liver (7).

Some clinical studies on the regulation of adiponectin have been performed. Reduced serum levels of adiponectin in obese compared with nonobese subjects and negative correlations between adiponectin and body mass index (BMI) have been reported (8–11). However, the relationship between BMI and circulating adiponectin becomes statistically insignificant if factors related to insulin sensitivity are taken into account (12, 13), suggesting that obesity *per se* does not influence serum adiponectin concentrations. Furthermore, serum concentrations of adiponectin have been found to be inversely correlated with insulin sensitivity in both nonobese (12, 13) and obese (9, 14, 15) subjects as well as in patients with type 2 diabetes mellitus (10, 14).

Very little is known about the secretion of adiponectin from adipose tissue and its role in the regulation of the amount of circulating adiponectin. Motoshima *et al.* (16) investigated adiponectin secretion from human fat cells, but no measurement of circulating adiponectin was performed. In the present study we have investigated the sc adipose tissue secretion rate, adipose mRNA expression, and serum concentrations of adiponectin in a large study population with a wide range of insulin sensitivity and consisting of both nonobese and massively obese women. We addressed the following as yet unanswered question: How important is adipose secretion of adiponectin for the corresponding serum concentration of the protein in obesity and insulin resistance?

Subjects and Methods

The study group consisted of 77 obese and 23 nonobese subjects recruited by local advertising. Their age was 20–50 yr. Obesity was defined according to the WHO criterion (BMI, >30 kg/m^2). All subjects were apparently healthy and did not take any regular medication. None had a history of alcohol overconsumtion. None of the women was postmenopausal, completely sedentary, or involved in athletics. All subjects were examined in the morning (at ~0800 h) after an overnight fast. The examination was made in the middle of the menstruation cyclic according to self report. Height and weight were measured, and body fat (percentage) was determined by bioimpedance (model TBF 305, Tanika, Japan). A venous blood sample was obtained for the measurement of plasma levels of glucose and insulin at the hospital's routine chemistry laboratory. In addition, serum levels of adiponectin were measured using an RIA method (Linco Research, Inc., St. Charles, MO) and were expressed as micrograms per milliliter. The homeostasis model

Abbreviations: BMI, Body mass index; GAPDH, glyceraldehyde-3-phosphate dehydrogenase; H, high insulin sensitivity subgroup; HOMA, homeostasis model assessment; I, intermediate insulin sensitivity subgroup; L, low insulin sensitivity subgroup.

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assessment (HOMA) model was used to calculate *in vivo* insulin sensitivity according to the formula: fasting plasma glucose (mM) × fasting plasma insulin (mU/liter) × 22.5^{-1} (17). Finally, a sc fat biopsy (1–2 g) was obtained from the umbilical region under local anesthesia. The adipose tissue was cut into small pieces (10–25 mg) and then incubated at 37 C (3.0 ml medium/300 mg tissue) in a medium consisting of sterile Krebs-Ringer phosphate buffer (pH 7.4), endotoxin-free BSA (4 g/100 ml), and glucose (1 mg/ml), with air as the gas phase. After a 2-h incubation, a 1-ml aliquot of medium was removed and stored at −70 C for subsequent analysis of adiponectin using the RIA described above, and the incubated adipose tissue was removed for organic extraction and determination of its total lipid content (18). In methodological experiments, pieces of adipose tissue from three subjects were incubated as described above for various periods of time (60 min to 3 h). The release of adiponectin was linear with incubation time for at least 2 h, as shown in Fig. 1. Adiponectin release is expressed as nanograms per gram of lipid per 2 h.

In a subgroup of the subjects, a 300-mg piece of adipose tissue was immediately stored at −70 C for subsequent analysis of adiponectin mRNA. Adipose tissue total RNA was extracted using the RNeasy total RNA kit (Qiagen, Hilden, Germany). The concentrations of RNA were determined spectrophotometrically at 260 nm. The absorption ratios at 260–280 nm were between 1.7–1.9. The RNA samples were stored at −70 C for subsequent cDNA synthesis from total adipose tissue RNA. The levels of adiponectin and glyceraldehyde-3-phosphate dehydrogenase (GAPDH) mRNA were measured twice in triplicate using a real-time PCR (iCycler, Bio-Rad, Hercules, CA). The primers used for adiponectin were GGTCTCGAA CTCCTGGCCTA (sense) and TGAGATATC-GACTGGGCATGGT (antisense), and those used for the reference gene GAPDH were CACATGGCCTCCAAGGAGTAAG (sense) and CCAG-CAGTGAGGGTCTCTCT (antisense). The length of the PCR amplicons was 94 bp for adiponectin and 82 bp for GAPDH. Adiponectin mRNA values were expressed as ratios of adiponectin/GAPDH mRNA, assuming that GAPDH is a housekeeping gene that is not regulated by factors such as obesity and insulin sensitivity. We chose GAPDH because it is constitutively expressed in various tissues and has been used widely as an internal RNA control for Northern blotting, ribonuclease protection, and RT-PCR.

Values are given as the mean ± SEM. Unpaired *t* test, ANOVA, Fisher's test (for *post hoc* analysis of ANOVA data), and simple regression analysis were used for statistical comparisons. Values for plasma insulin and HOMA index were not normally distributed and therefore were logarithmically transformed before comparisons. Standard computer software was used for the statistical analysis.

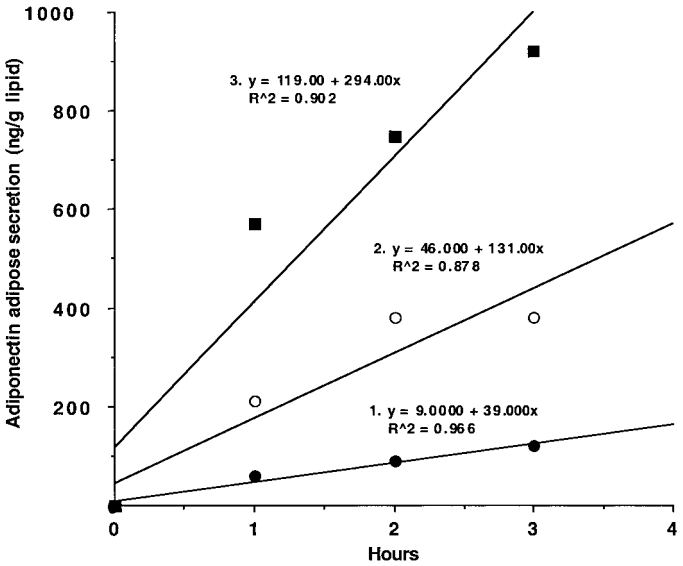

FIG. 1. Methodological experiment showing adipose tissue secretion of adiponectin from three subjects analyzed by simple regression analysis.

The study was approved by the ethics committee of Huddinge University Hospital. All women gave informed consent to participate.

Results

The clinical data of the obese and nonobese subjects are shown in Table 1. The study groups were of similar age. However, as expected, the obese subjects showed higher levels of BMI, percent body fat, plasma values of insulin and glucose, as well as HOMA index. In Fig. 2, serum levels and adipose tissue secretion levels of adiponectin are demonstrated. No difference in serum adiponectin concentration between obese and nonobese subjects was found (14.0 ± 0.8 *vs.* 13.1 ± 0.9 μg/ml; $P = 0.55$). In contrast, the sc adipose secretion rate of adiponectin was reduced in obese compared with nonobese subjects (309 ± 13 *vs.* 382 ± 28 ng/g lipid·2 h; $P = 0.009$).

To investigate the influence of insulin sensitivity on serum concentrations and adipose secretion rate of adiponectin, all subjects were grouped together, and the whole cohort was divided into tertiles according to the HOMA index. As seen in Table 2, except for age, all clinical parameters analyzed were different between the subgroups. Furthermore, as shown in Fig. 3, both the serum concentration and the adipose tissue secretion rate of adiponectin were influenced by insulin sensitivity. With respect to serum adiponectin, the concentrations were 16.7 ± 1.3, 14.6 ± 1.1, and 10.4 ± 0.9 in the high (H), intermediate (I), and low (L) insulin sensitivity subgroups, respectively (by ANOVA: $P < 0.001$; by *post hoc* analysis: H *vs.* I, $P = 0.18$; H *vs.* L, $P = 0.0001$; I *vs.* L, $P = 0.008$). For adipose secretion, the corresponding rates were 365 ± 24 (H), 313 ± 19 (I), and 294 ± 16 (L) in the three subgroups, respectively (by ANOVA: $P < 0.037$; by *post hoc* analysis: H *vs.* I, $P = 0.07$; H *vs.* L, $P = 0.01$; I *vs.* L, $P = 0.50$). After dividing the HOMA index into quartiles, there was still a significant difference between the groups for both serum levels ($P = 0.0001$, by ANOVA) and adipose secretion levels ($P = 0.01$, by ANOVA). In simple regression analysis, both adiponectin serum levels ($r = -0.37$; $P = 0.0002$; adjusted $r^2 = 0.13$) and adipose secretion rate ($r = -0.30$; $P = 0.0026$; adjusted $r^2 = 0.08$) were correlated with the HOMA index.

The influence of sc adipose tissue secretion rate on serum concentrations of adiponectin was investigated by simple regression analysis in all subjects as well as in the various subgroups of insulin sensitivity (Table 3). In the whole study group, a significant correlation between serum levels and adipose secretion rates was found. The adjusted r^2 for this relationship was 0.08 ($P < 0.01$). However, with respect to

TABLE 1. Clinical data in nonobese and obese women

	Nonobese	Obese	*P*
n	23	77	
Age (yr)	34 ± 2	37 ± 1	0.13
BMI (kg/m^2)	24 ± 1	37 ± 1	<0.0001
Body fat (%)	32 ± 1	56 ± 1	<0.0001
P glucose (mmol/liter)	4.7 ± 0.1	5.4 ± 0.1	<0.0001
Log P insulin (mU/liter)	0.74 ± 0.02	1.07 ± 0.02	<0.0001
Log HOMA index	0.07 ± 0.03	0.44 ± 0.02	<0.0001

Values (mean ± SEM) are compared using Student's unpaired *t* test. P, Fasting plasma.

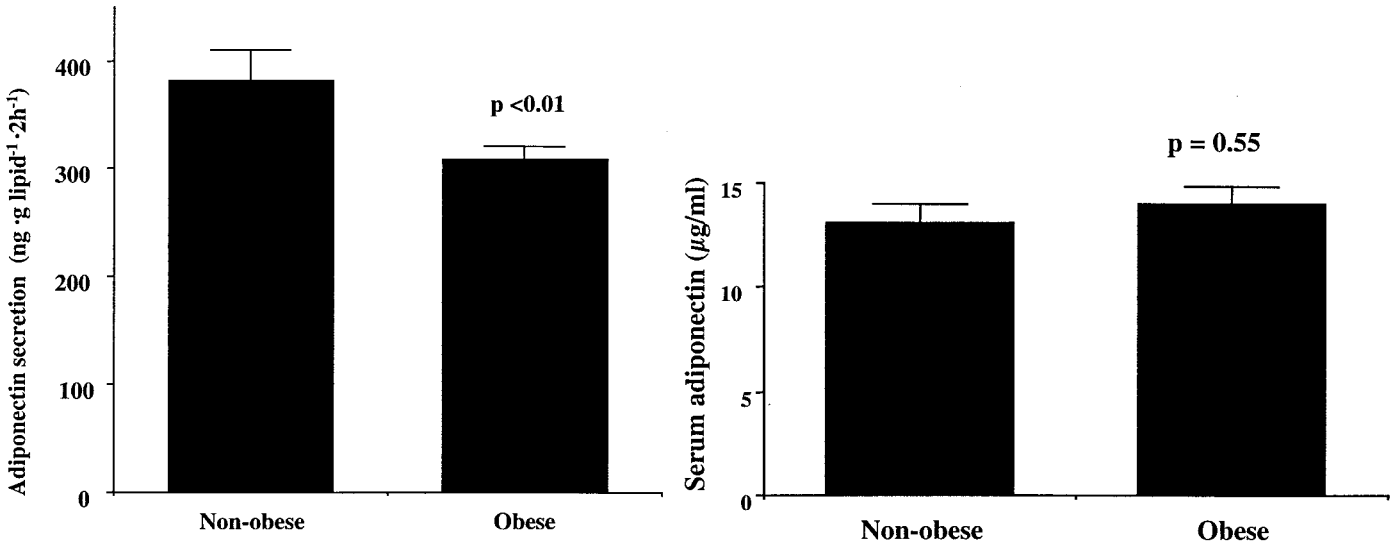

FIG. 2. Serum concentration and adipose tissue secretion rate of adiponectin in nonobese and obese subjects. Values are the mean ± SE, and data were compared by *t* test.

TABLE 2. Clinical data according to HOMA insulin sensitivity

	Insulin sensitivity (tertiles)			
	High	Intermediate	Low	*P*
N	33	33	32	
Age (yr)	36 ± 1	36 ± 1	37 ± 1	0.65
BMI (kg/m^2)	28 ± 1	36 ± 1	38 ± 1	<0.0001
Body fat (%)	40 ± 2	55 ± 2	57 ± 2	<0.0001
P glucose (mmol/liter)	4.8 ± 0.1	5.2 ± 0.1	5.7 ± 0.1	<0.0001
Log P insulin (mU/liter)	0.76 ± 0.01	1.00 ± 0.01	1.25 ± 0.02	<0.0001
Log HOMA index	0.09 ± 0.02	0.36 ± 0.01	0.66 ± 0.02	<0.0001

Values (mean ± SEM) are compared using ANOVA. P, Fasting plasma.

insulin sensitivity, serum concentrations and secretion rates of adiponectin were correlated ($P < 0.05$) in the H subgroup only; the adjusted r^2 was 0.16 (Fig. 4).

We made an approximate estimate of adiponectin turnover in the nonobese group using the methods described for leptin (19). The calculation was based on the following assumptions: 1) the lipid content of adipose tissue is 0.8 times the tissue weight; 2) abdominal sc adipose tissue production rate of adiponectin is representative for all adipose depots in nonobese women (data in Ref. 16 show 30% differences in secretion rates between the visceral and the sc depots, but in women, the visceral fat depot is only a minor component of total fat, whereas the sc area is by far the largest region); 3) *in vitro* secretion rates of adiponectin are about the same as *in vivo* secretion rates; and 4) adiponectin concentrations in plasma and serum are almost identical. The total adiponectin production rate (nanograms per kilogram of total fat mass per hour) was: 382 × (mean *in vitro* production rate) × 0.32 (mean body fat fraction) × 66,000 (mean body weight in g) ÷ 0.8 (tissue lipid fraction) ÷ 2 (incubation time) = 5,042,400. The total plasma pool of adiponectin (nanograms) is 66 × 37 (plasma pool size) × 13,100 (serum adiponectin concentration) = 31,990,200. The plasma adiponectin fractional turnover (k) is 5,042,400 ÷ 31,990,200 = 0.158. The plasma adiponectin half-life is ln 2/k = 2.5 h.

Total body fat production rate of adiponectin (ng·kg total fat mass·h^{-1}) was also investigated in relation to obesity and insulin resistance. It was found that total body fat production of adiponectin was about twice as high in obese women (9.1 ± 0.5 mg) as compared to nonobese women (4.2 ± 0.4 mg) ($P < 0.0001$). In relation to insulin sensitivity, the values of adiponectin total body fat production were 6.2 ± 0.7 (high), 8.9 ± 0.7 (intermediate), and 9.1 ± 0.7 (low) in the three groups of insulin sensitivity ($P = 0.007$). In simple regression analysis, adiponectin body fat production correlated with insulin sensitivity as measured by HOMA-index ($r = 0.31$, $P = 0.002$, adjusted $r^2 = 0.09$).

Finally, adipose tissue mRNA adiponectin in relation to the amount of GAPDH was measured in 18 subjects. They were selected from each of the HOMA tertiles; six obese subjects with low HOMA index, six obese subjects with high HOMA index, and six nonobese subjects with low HOMA index. All subjects were selected at random. As shown in Fig. 5, the relative amount of adiponectin mRNA (*i.e.* adiponectin/GAPDH) was lower in obese subjects with both low (8.5 ± 1.2) and high (8.1 ± 1.6) HOMA index than in nonobese subjects (16.3 ± 2.7; $P = 0.01$, by ANOVA). However, there was no difference between subjects with high compared with low HOMA index (8.1 ± 1.6 *vs.* 12.4 ± 1.8; $P = 0.15$, by *post hoc* analysis).

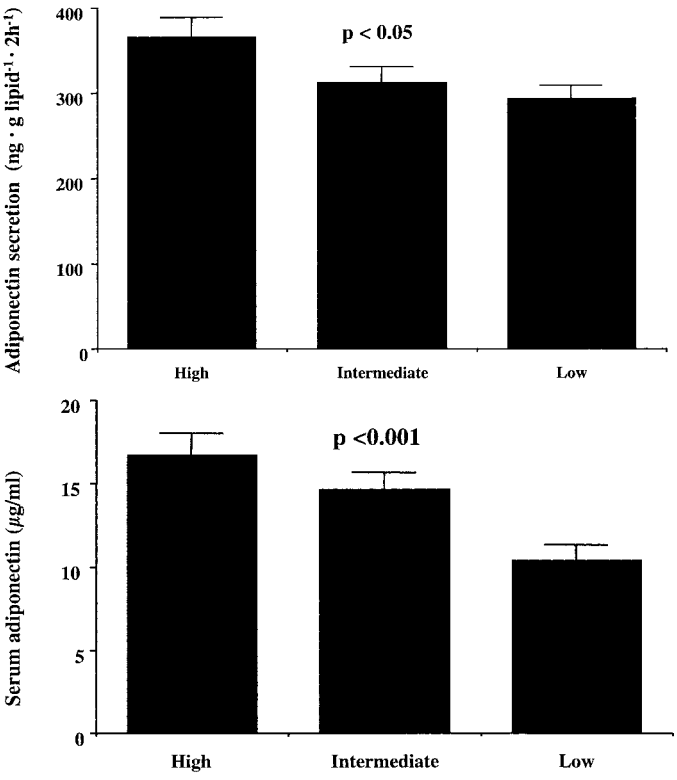

FIG. 3. Serum concentration and adipose tissue secretion rate of adiponectin in women with different levels of insulin sensitivity. Values are the mean ± SE, and data were compared by ANOVA.

TABLE 3. Correlations (according to regression analysis) between serum levels and adipose tissue secretion rate of adiponectin in all subjects and in subgroups of different levels of insulin sensitivity

	r	Adjusted r^2	*P*
All subjects	0.28	0.08	0.005
High insulin sensitivity	0.43	0.18	0.014
Intermediate insulin sensitivity	−0.13	0.02	0.47
Low insulin sensitivity	0.21	0.04	0.26

Discussion

This large study was designed to evaluate the influence of obesity and insulin sensitivity on the production of adiponectin in sc adipose tissue and the role of adiponectin secretion for the serum concentrations of the protein. Because gender might be a confounding factor, we only studied women. In obesity, a reduced adipose secretion rate, but no change in serum concentrations of adiponectin, was found. In contrast, insulin-resistant subjects had lower values of both adipose secretion rate and serum concentrations of adiponectin than did subjects with high insulin sensitivity. At first glance, the results with adiponectin in obesity seem at odds with previous findings of reduced plasma concentrations of adiponectin in this condition (8, 9). However, it has also been shown that the level of insulin sensitivity has a major impact on adiponectin levels in man (9, 12, 13) and that the degree of hypoadiponectemia in obesity is related to insulin resistance, rather than to body fat content (12–14).

It has previously been shown that both obesity (20) and type 2 diabetes (21) are associated with reduced mRNA expression of adiponectin in human adipose tissue. The present study confirms that adiponectin adipose tissue mRNA is lower in obese than in nonobese subject. In contrast, there was no additive effect of insulin sensitivity on gene expression, which suggests that both transcriptional and posttranscriptional mechanisms are determinants of adiponectin adipose secretion in obese or insulin-resistant humans.

The present findings deviate from those in the study by Motoshima *et al.* (16), who found that human omental, but not sc, adipose tissue secretion of adiponectin was negatively correlated to BMI. However, the difference may be more apparent than real. First, the previous study sample was relatively small, and only three subjects had BMI below 30 kg/m^2. Second, and more important, is that the earlier study used isolated fat cells that had been cultured for 12–24 h, whereas we used freshly isolated intact tissue pieces. Therefore, environmental or stromal factors, which could disappear during culture of isolated cells, could explain the differences in results.

To date it has not been known how important adipose tissue secretion of adiponectin is for regulating the circulating concentration of the protein. This is a relevant question because recent findings suggest that adiponectin is a true hormone acting through specific receptors in insulin target tissues, such as skeletal muscle and liver (7). To clarify this issue we made attempts to calculate adiponectin turnover *in vivo*. It should be stressed that turnover data are approximate, because they rely on several assumptions, such as the idea that regional variations in hormone secretion are relatively small (16) and *in vitro* secretion rates are similar to *in vivo* secretion rates. Nevertheless, the turnover rate seems very slow, because the plasma half-life is about 2.5 h. Most polypeptide hormones, including leptin, have plasma half-lives between 15 and 30 min (19, 22). This suggests that the rate of turnover of adiponectin is 5–10 times slower than that for most polypeptide hormones. As the rate of production also is slow, it is likely that the production rate of the hormone is not the major regulating factor for the high circulating hormone concentration. This theory is further supported by our findings of a rather weak (but significant) relationship between the secretion of adiponectin and the serum adiponectin level. The production rate could explain 8–16% of the interindividual variation in serum adiponectin if all or only the most insulin-sensitive women were investigated. Although the reason for the low level of correlation is unknown, it may be that factors other than adipose secretion, such as turnover and degradation, regulate serum concentrations of adiponectin. This assumption is based on studies of sc adipose tissue. By multiple regression analysis, it was recently reported that intraabdominal, but not sc, fat mass was related to adiponectin plasma concentrations, in addition to age and sex (13). However, sc adipose tissue is by far the most abundant fat depot in women. According to previous findings the *in vitro* rate of adiponectin secretion is about 30% higher in visceral than in sc adipose tissue (16). Despite this finding, the visceral fat depot is very small in comparison with the visceral depot (in particular in women). Therefore, the rate of adiponectin production is too slow to be the major regulator of the very large circulating pool of the

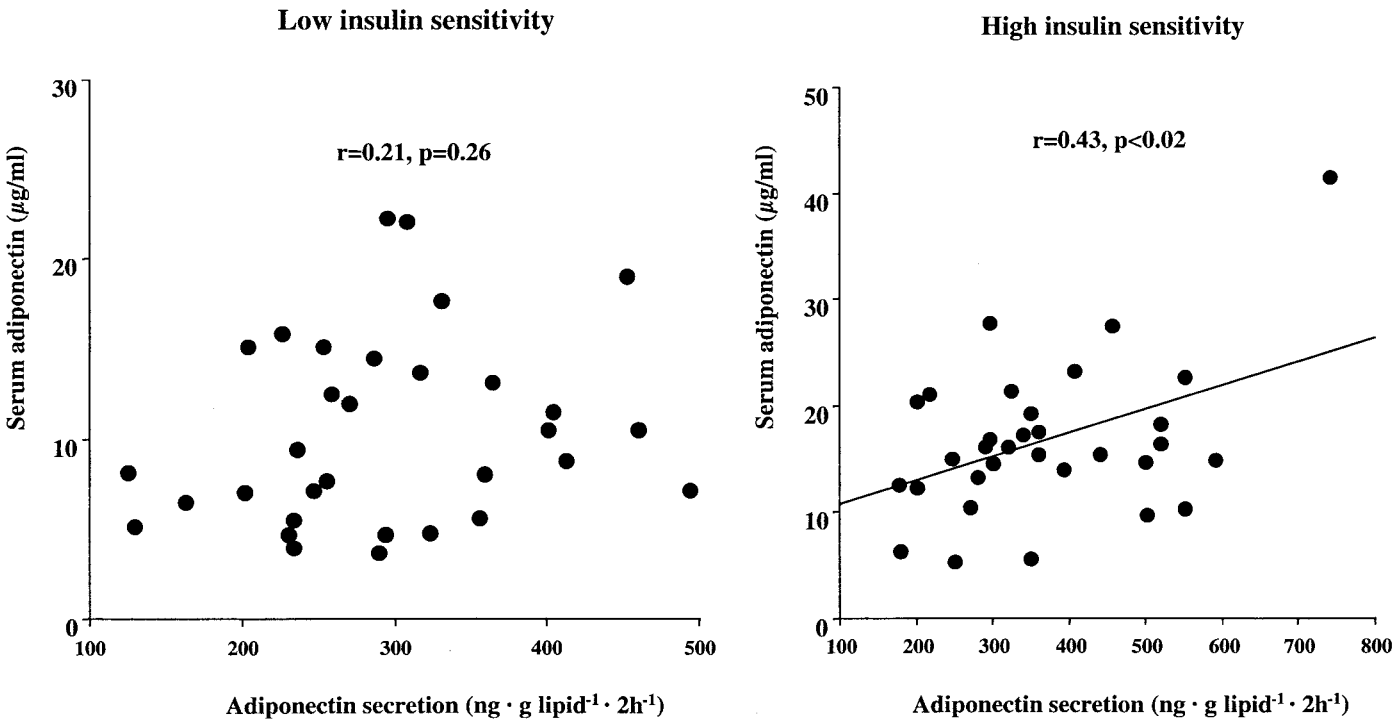

FIG. 4. Linear regression analysis of adipose tissue secretion rate *vs.* serum concentration of adiponectin in women with low (*left graph*) and high (*right graph*) insulin sensitivity.

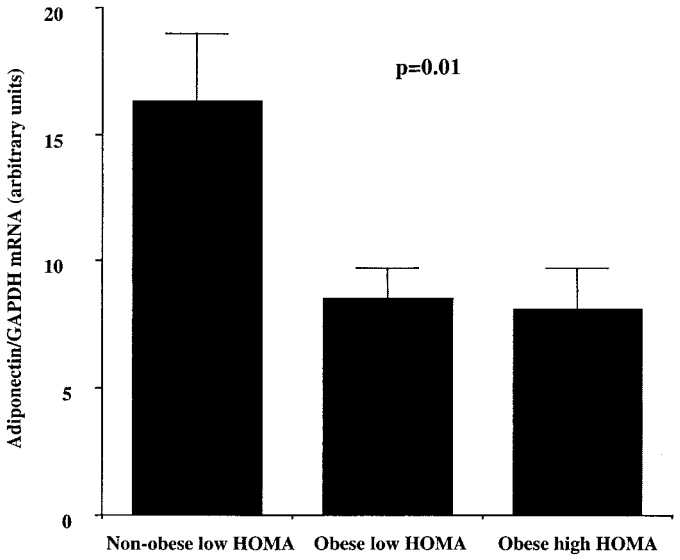

FIG. 5. Adiponectin mRNA in relation to GAPDH mRNA in adipose tissue from six nonobese women with high insulin sensitivity, six obese women with high insulin sensitivity, and six obese women with low insulin sensitivity. Values are the mean ± SE, and data were compared by ANOVA.

hormone, even if an "extra 30%" production from visceral fat is considered.

It is not likely that diurnal variations in adiponectin turnover have influenced the results in an important way. The serum adiponectin concentration is highest in the morning, when our subjects were investigated, and lowest during the night, but the difference between these concentrations is small (~20%) (23). To study the total body fat production of adiponectin, it is necessary to express the secretion rate in relation to cell lipid content. We cannot exclude that the use of a different denominator, *e.g.* cell number or protein content, could have influenced the results.

It is of interest to observe that the estimated total body adiponectin production in obese women was two times higher than in nonobese women, whereas the circulating levels of the protein were similar in the two groups. Furthermore, insulin-resistant subjects had increased total body production of adiponectin despite decreased serum concentrations of the hormone. However, per weight unit of adipose tissue adiponectin production was decreased in obese, as well as in insulin-resistant, subjects. Taken together, these findings suggest an ineffective regulation of adiponectin in these conditions. It appears that upon body fat accumulation and insulin resistance development, there is not enough production of adiponectin to rise the circulating hormone level.

In conclusion, this study shows that adiponectin secretion from sc adipose tissue is reduced in obesity and insulin resistance when expressed per tissue weight, whereas total body fat production rate is increased. Moreover, sc adipose tissue secretion plays only a minor role in variations in circulating concentrations of adiponectin, probably because the turnover rate of the protein is slow in man.

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