Restoration of Adiponectin Pulsatility in Severely Obese Subjects After Weight Loss

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Diurnal variations of adiponectin levels have been studied in normal-weight men and in diabetic and nondiabetic obese subjects, but no data have been reported in obese subjects after weight loss. We collected blood samples at 1-h intervals over 24 h from seven severely obese subjects before and after massive weight loss consequent to surgical operation (bilio-pancreatic diversion [BPD]) to measure adiponectin, insulin, glucose, and cortisol levels. Insulin sensitivity was assessed by euglycemic-hyperinsulinemic clamp (M value). Studies of diurnal variations and pulsatility of adiponectin, insulin, and cortisol were performed. The pulsatility index (PI) of adiponectin increased after BPD from 0.04 to 0.11 μg/min (P = 0.01). Insulin PI significantly increased after the operation (1.50 vs. 1.08 pmol·l−1·min−1, P = 0.01), while cortisol PI did not significantly change. The adiponectin clearance rate changed from 0.001 ± 10−4·min−1 before BPD to 0.004 ± 8·10−4·min−1 after BPD (P = 0.03). Insulin clearance increased from 0.006 ± 6·10−4·min−1 before BPD to 0.009 ± 4·10−4·min−1 after BPD (P = 0.02). The M value doubled after surgery (27.08 ± 8.5 vs. 53.34 ± 9.3 μmol·kgFFM−1·min−1; P < 0.001) becoming similar to the values currently reported for normal-weight subjects. In conclusion, in formerly severely obese subjects, weight loss paired with the reversibility of insulin resistance restores homeostatic control of the adiponectin secretion, contributing to the reduction of cardiovascular risk already described in these patients. Diabetes 53:939–947, 2004

Recent advances in the biology of adipose tissue indicate that it is not simply an energy storage organ but also a secretory organ, producing a variety of bioactive substances, including leptin, tumor necrosis factor (TNF)-α, resistin, and adiponectin, thus acting as an endocrine organ. These adipocyte-specific proteins, termed adipokines, present a variety of local, peripheral, and central effects. It has been shown that the adipose tissue secretes metabolites such as non-esterified fatty acids (NEFAs), glycerol, and hormones (1) in a pulsatile fashion, similar to leptin. The regulation of this pulsatility seems to be mediated by hormonal (2) or neural (2,3) mechanisms. Insulin plays a critical role in the regulation of both the hormonal and metabolic activity of the adipocytes.

Higher absolute leptin levels coupled with blunted relative diurnal excursions and dampened pulsatility have been found in obese subjects (4). Similarly, insulin pulse amplitudes are restored (5). Weight loss restores leptin pulsatility (4) and reverses insulin resistance (6).

Recently, diurnal variations in circulating levels of adiponectin in diabetic and nondiabetic obese subjects (7) and in healthy normal-weight male human subjects have been investigated (3). Hotta et al. (7) did not observe any daily changes in circulating levels of adiponectin in obesity. In normal-weight subjects, Gaviria et al. (3) found an ultradian pulsatility as well as a diurnal variation in adiponectin plasma levels with a significant decline at night, reaching a nadir in the early morning. However, to the best of our knowledge no data have been reported in the literature regarding the diurnal pulsatility of adiponectin in obese subjects after weight loss.

In contrast, a few studies have investigated the effect of weight loss on fasting adiponectin plasma levels. Fasting circulating adiponectin concentrations have been reported to increase after weight loss obtained by either gastric partition in obese subjects (8) or Roux-en-Y gastric bypass surgery in morbidly obese subjects (9). More recently, a dietary intervention study showed that weight loss in obese nondiabetic subjects was associated with a significant increase in circulating levels of adiponectin (10).

Since no data are available in the literature concerning the ultradian rhythm and pulsatility of adiponectin in obese subjects before and after weight loss, the present study was undertaken to evaluate the 24-h adiponectin profile in morbidly obese subjects before and after weight loss as a result of malabsorptive bariatric surgery. In addition, a number of determinants of the daily adiponectin pattern were also investigated.

RESEARCH DESIGN AND METHODS

Study protocol. The study groups consisted of seven severely (BMI >40 kg/m2) obese female subjects studied on two separate occasions: before and 2 years after bilo-pancreatic diversion (BPD). None had impaired glucose tolerance, diabetes, or any other endocrine or nondiabetic disease. At the time of the baseline study, all subjects were on an ad lib diet, with the

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AUC, area under the curve; BPD, bilo-pancreatic diversion; EHC, euglycemic-hyperinsulinemic clamp; FFM, fat-free mass; HPA, hypothalamus-pituitary-adrenal; NEFA, nonesterified fatty acid; PI, pulsatility index; TBW, total body water; TNF, tumor necrosis factor.

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TABLE 1
Anthropometric characteristics of the subjects studied

<table>
<thead>
<tr>
<th></th>
<th>Before BPD</th>
<th>After BPD</th>
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<tbody>
<tr>
<td>BMI (kg/m²)</td>
<td>57.50 ± 9.84</td>
<td>28.96 ± 0.94</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>168.50 ± 32.65</td>
<td>84.50 ± 6.028</td>
</tr>
<tr>
<td>FFM (kg)</td>
<td>93.32 ± 26.53</td>
<td>68.17 ± 10.58</td>
</tr>
<tr>
<td>Fat mass (kg)</td>
<td>75.17 ± 9.06</td>
<td>13.82 ± 6.39</td>
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</table>

Data are means ± SD.

following average composition: 60% carbohydrate, 30% fat, 10% protein (at least 1 g/kg body wt). This dietary regimen was maintained for 1 week before the study. The nature and purpose of the investigation were explained to all subjects before they agreed to participate in the study, which complied with the guidelines of the hospital ethics committee. The subjects were studied on 2 separate days, once for the assessment of insulin secretion during a standardized 24-h period and once for the determination of insulin sensitivity using the glucose clamp method.

BPD. This essentially malabsorptive surgical procedure (11) consists of an ~60% distal gastric resection with stapled closure of the duodenal stump. The residual volume of the stomach is ~300 ml. The small bowel is transected at 2.5 m from the ileocecal valve, and its distal end is anastomosed to the remaining stomach. The proximal end of the ileum, comprising the remaining small bowel carrying the bilio-pancreatic juice and excluded from food transit, is anastomosed in an end-to-side fashion to the bowel 50 cm proximal to the ileocecal valve. Consequently, the total length of absorbing bowel is brought to 250 cm, the final 50 cm of which, the so-called common channel, represents the site where ingested food and bilio-pancreatic juices mix. Restrictive bariatric surgery, such as a long gastroplasty, allows a 20- to 30-ml pouch limit for the site where ingested food and bilio-pancreatic juices mix. These low-pass filtered time series were used to study the long-term variations on selected time scales. Serum levels of adiponectin were measured by microparticle enzyme immunoassay (Abbott, Pasadena, CA) with a sensitivity of 1 μU/ml and an intra-assay CV of 6.2%. Plasma adiponectin levels were measured using radioimmunoassay (Linco, St. Charles, MO) with a sensitivity of 1 μg/ml and an intra-assay CV of 6.2%. Fasting plasma leptin was assayed by radioimmunoassay for human leptin (Phoenix Pharmaceuticals, Phoenix, AZ). Intra- and interassay CVs were 4.2 and 4.5%, respectively. The sensitivity of the method was 0.5 ng/ml. All samples for each subject were assayed every hour at the same time.

Diurnal variability analysis. According to the method previously applied by Gravila et al. (3), Fourier analysis (20) was applied to the 24-h hormonal time series to study fluctuations on selected time scales. Serum levels of adiponectin, insulin, and cortisol for each subject were first low-pass filtered over a frequency range of 0–0.1 cycles/h to extract the low-frequency components. These low-pass filtered time series were used to study the long-term variations. Each filtered dataset was rescaled so that the 24-h average was set equal to 100%, and data at each time point were defined as a percentage of the 24-h average. Group averages for all six subjects were then calculated for each of the three hormones, adiponectin, insulin, and cortisol.

**FIG. 1.** Correlation between fasting plasma adiponectin and fasting plasma leptin levels before and after BPD.
Pulsatility analysis. Pulsfit, a computerized algorithm (21), was used to identify the pulses in the 24-h time series. Pulsfit uses a strict mathematical definition of a pulse as an instantaneous rise followed by an exponential decline to model circulating hormone measurements. The optimal peak heights and clearance rate are determined by least squares. The optimal peak location is determined by stepwise regression, and the optimal peak number (peak frequency) by minimizing the predictive error (using the minimum generalized cross-validation score index). The program returns a pulsatility index (PI), which measures the "pulsiness" of a series. Specifically, the PI is defined as the standard deviation of the positively constrained, optimal, discrete deconvolution of the logarithm of the circulating hormone measurements.

Before using the Pulsfit program, the experimental hormone concentration time series (24 points: 1 point per hour) was fitted by cubic splines in order to obtain an estimate of circulating levels every 10 min (while the experimental data were obtained every hour) and to optimize pulses identification. The fitting procedure was obtained using the "csaps" MatLab function, where \( y \times z \) = \( csaps(x,y,xx) \) return the values at \( xx \) of the cubic smoothing spline for the given data \((x,y)\) and depending on the smoothing parameter \( p \) from 0 to 1. For \( p = 0 \), this is the least-squares straight line fit to the data; while at the other extreme, i.e., for \( p = 1 \), this is the "natural" or variational cubic spline interpolant. In this study, \( p \) was assumed to be 0.995.

Statistical analysis. Data are reported as means ± SD. Correlations between variables were tested with nonparametric Spearman’s correlation analysis \((r_s)\). We performed the Wilcoxon test to compare data from the two groups. The relationship between the independent variables (fat mass, \( M \) values, and cholesterol, HDL cholesterol, and triglyceride levels) and the dependent variable (plasma adiponectin fasting levels) was analyzed by stepwise backward multiple regression analysis. The validity of the regression model was checked using standard tests. These included assessing the distribution of the residuals, testing for normality, and checking the linearity assumptions in the model by means of standard scatter plots. Data analyses were performed with SPSS statistical software (SPSS, Chicago, IL). Two-sided \( P < 0.05 \) was regarded as significant. The areas under the curve (AUCs) of the insulin or adiponectin time courses were calculated using a trapezoidal rule.

Cross-correlation analysis. To assess the temporal relationships of diurnal variations among the three hormones studied, a standard cross-correlation analysis (22) on a paired low-pass filtered time series from each subject was performed. Each graph represents the mean (——) ± SEM (- - -) of the values measured in the seven subjects studied.

### Table 2

<table>
<thead>
<tr>
<th>Variables</th>
<th>( \beta )-Coefficient</th>
<th>( P )</th>
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<tbody>
<tr>
<td>Fat mass (kg)</td>
<td>-0.879</td>
<td>0.0001</td>
</tr>
<tr>
<td>( M ) value (mg · kg FFM(^{-1}) · min(^{-1}))</td>
<td>-0.996</td>
<td>0.030</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>0.737</td>
<td>NS</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dl)</td>
<td>-0.227</td>
<td>NS</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>-0.119</td>
<td>NS</td>
</tr>
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**FIG. 2.** Time courses of plasma adiponectin, insulin, glucose, and cortisol levels before and after BPD. Each graph represents the mean (——) ± SEM (- - -) of the values measured in the seven subjects studied.

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used. The cross-correlation functions were then averaged overall for the subjects studied, and the lag relationships among the measured hormones were calculated.

RESULTS

BMI and metabolic parameters. The average preoperative BMI was 57.5 ± 9.8 kg/m². BMI was dramatically reduced after surgery to 28.5 ± 0.9 kg/m². A significant decrease in FFM was observed together with a decrease in fat mass (Table 1).

Plasma NEFAs levels decreased from 0.417 ± 0.154 mmol/l to 0.172 ± 0.067 mmol/l postoperatively (P < 0.01). Circulating triglycerides dropped from 1.30 ± 0.88 to 0.93 ± 0.25 mmol/l (P < 0.001) after BPD. A similar trend was observed for plasma cholesterol (5.21 ± 0.78 to 3.40 ± 0.37 mmol/l; P < 0.01). A significant (P < 0.01) increase in HDL cholesterol was observed simultaneously (from 1.02 ± 0.18 to 1.28 ± 0.20 mmol/l). Fasting plasma insulin dropped from 129.6 ± 18.6 to 27.6 ± 3.6 (P = 0.02) after BPD.

EHC. The target plasma glucose concentration in the subjects studied before and after bariatric surgery showed no statistically significant differences within each group examined. In all patients the plasma glucose concentration variation in the last 40 min of the 2-h clamp was <10%, and a steady-state glucose infusion rate was achieved in all case subjects in the last 40 min of the EHC. The M value doubled after surgery (27.08 ± 8.5 vs. 53.34 ± 9.3 μmol · kg⁻¹ · min⁻¹; P < 0.001), becoming similar to the values currently reported (23) in healthy subjects.

The average plasma insulin levels during the last 40 min showed no statistically significant differences in the two groups (544.51 ± 23.16 pmol/l before and 552.01 ± 17.64 pmol/l after BPD). Nevertheless, the lowest value reached was >500 pmol/l; therefore, it is conceivable that the hepatic glucose production was inhibited by insulin.

Fasting adiponectin. Mean preoperative fasting adiponectin concentration was 8.82 ± 2.41 g/ml and increased in response to weight loss after BPD in all subjects to 18.97 ± 7.36 g/ml (P < 0.001). The natural logarithm of the plasma adiponectin level correlated negatively with fat mass (before BPD y = 0.0294x + 4.3481, R² = 0.90; and after BPD y = -0.057ix + 3.6758; R² = 0.75), meaning that for each kilogram of fat mass lost there was an increase in plasma adiponectin concentration of the order of ~6%. Plasma adiponectin concentration, expressed as the natural logarithm, correlated positively with insulin-stimulated whole-body glu-
cose uptake (M value) both before (y = 1.5709x − 2.2052; 
R² = 0.87) and after (y = 0.8235x − 3.551; R² = 0.79) BPD. 
Figure 1 shows the correlation between fasting adiponec-
tin and leptin plasma levels. Experimental data were 
fit by two different regression equations (y = −4.5704 + 
102.83, R² = 0.95 and y = −0.487x + 27.407, R² = 0.77) 
before and after BPD, respectively.

Stepwise backward multiple linear regression analysis 
showed that the best-fit model to predict plasma adiponec-
tin fasting levels included fat mass (P = 0.0001) and 
M values (P = 0.03). In contrast, total cholesterol, HDL cholesterol, and triglycerides levels were not included in 
the model (Table 2).

Diurnal variability analysis. The time courses of plasma concentrations of adiponectin, insulin, glucose, and corti-
sol (±SEM) are reported in Fig. 2.

The AUC of the adiponectin levels before BPD, com-
puted using a trapezoidal rule, was 47 ± 2 µg · h⁻¹ · ml⁻¹ and increased significantly (P = 0.03) to 135 ± 24 after 
BPD. In contrast, the insulin AUC was significantly (P = 
0.02) reduced after BPD (from 3,564 ± 870 to 1,032 ± 36 
pmol · h⁻¹ · 1⁻¹). No significant change was observed in 
the cortisol AUC (from 3,305 ± 1,376 to 3,343 ± 853 nmol · h⁻¹ · 1⁻¹). Plasma insulin concentrations were definitely higher 
in obese than in lean subjects, while adiponectin levels 
were lower. Levels of circulating adiponectin increased progressively during each meal and decreased to trough 
levels within 1–2 h. The peaks of the levels of circulating 
insulin and glucose after each meal were better identifi-
able after weight loss, although markedly lower in the case 
of insulin.

The maximum diurnal variation in insulin levels, calcu-
lated as the difference between the mean peak and trough 
values, was 414.0 ± 98.4 pmol/l before BPD and 174.6 ± 
16.8 pmol/l after BPD (P = 0.04). Cortisol levels progres-
sively increased during the morning, peaking in the late 
morning. However, while in obese subjects cortisol levels 
were stable around the peak value until early afternoon, in 
previously obese subjects a continuous decline of the 
circulating concentration was observed with a nadir in the 
early night. The nadir was also present in the obese state. 
The maximum diurnal variation in cortisol concentration, 
calculated as the difference between the mean peak and 
trough values, was 280 ± 130 nmol/l before BPD and 373 ± 
150 nmol/l after BPD (P = NS).

Figures 3, 4, and 5 show the percentage of variation for 
adiponectin, insulin, and cortisol, respectively, averaged
for all seven subjects before and after BPD and suggest diurnal patterns.

Adiponectin values were higher during the day, with a peak in the late morning. After the peak level was reached there was minimal daytime variation, with adiponectin slightly decreasing during the late afternoon in BPD patients until midnight and rising again during the early morning. The subjects in the obese state showed no variations in adiponectin plasma concentration fluctuations during the evening and night.

The maximum diurnal variation of adiponectin levels was $2.41 \pm 0.32 \, \mu g/ml$, representing $27.31 \pm 2.26\%$ of the mean 24-h adiponectin level before BPD and $12.19 \pm 2.85 \, \mu g/ml$ after BPD ($P = 0.01$).

**Cross-correlation analysis.** The maximum values of the mean cross-correlation coefficients were observed in the pair cortisol-adiponectin before BPD (74%) and after BPD (67%), with cortisol preceding the 24-h adiponectin fluctuation by 50 min on average. The influence of long-term insulin fluctuation on adiponectin was largely different before (lag period 2 min and coefficient 55%) than after (60 min and 70%) BPD.

**Ultradian variability (pulsatility) analysis.** Typical results obtained by the cubic smoothing spline on an original time series of adiponectin from one typical subject before and after BPD are shown in Figs. 6 and 7, respectively. This mathematical procedure was needed to optimize the Pulsefit performance.

The adiponectin PI, defined as the standard deviation of the instantaneous secretion rate, increased significantly ($P = 0.01$) from $0.04 \, \mu g/min$ before BPD to $0.11 \, \mu g/min$ after BPD.

The PI of insulin increased significantly after the surgical operation ($1.50 \, \text{vs.} \, 1.08 \, \text{pmol/l/min}, P = 0.01$). The adiponectin clearance rate changed from $0.001 \pm 1 \cdot 10^{-4} \cdot \text{min}^{-1}$ before BPD to $0.004 \pm 8 \cdot 10^{-4} \cdot \text{min}^{-1}$ after BPD ($P = 0.03$). The insulin clearance rate increased from $0.006 \pm 6 \cdot 10^{-4} \cdot \text{min}^{-1}$ before BPD to $0.009 \pm 4 \cdot 10^{-4} \cdot \text{min}^{-1}$ after BPD ($P = 0.02$).

The cortisol PI increased, although not significantly, after BPD from $1.05 \pm 0.65$ to $1.35 \pm 0.71 \, \text{nmol} \cdot \text{l}^{-1} \cdot \text{min}^{-1}$. The cortisol clearance rate changed from $0.002 \pm 7.9 \cdot 10^{-5} \cdot \text{min}^{-1}$ to $0.004 \pm 4 \cdot 10^{-4} \cdot \text{min}^{-1}$.

**DISCUSSION**

The present study is the first report showing the 24-h adiponectin pulsatility pattern in morbidly obese subjects.
before and after surgically induced weight loss. The major findings of this investigation are that formerly morbidly obese subjects who underwent malabsorptive bariatric surgery, with a subsequent dramatic weight loss, showed a significant increase in plasma adiponectin AUC, a decrease in plasma insulin AUC, and a significant increase in the pulsatility of both adiponectin and insulin. The cortisol pulsatility did not change significantly after BPD.

A close relationship was also observed between plasma adiponectin concentration and insulin sensitivity as well as fat mass, as a measure of adiposity. Furthermore, fasting circulating levels of adiponectin negatively correlated with leptin concentrations, showing that the previous observation in normal-weight and obese subjects (24) is also applicable to severe obesity and the postobese state. However, the correlation was more significant before than after BPD, suggesting that weight loss influences leptin more than adiponectin. The major determinants of plasma adiponectin levels were the fasting plasma concentrations of insulin, the insulin-mediated whole-body glucose uptake, and fat mass. These findings confirm previously reported data showing that plasma adiponectin levels are negatively associated with percentage of body fat, visceral fat, and subcutaneous abdominal fat, and levels of insulin and leptin (25,26) and that independent determinants of low plasma adiponectin concentrations in
obesity are sex, age, BMI, insulin resistance, and HDL cholesterol (27). Furthermore, in a case-control series in the Pima Indian population, the baseline concentration of adiponectin was significantly lower in case than in control subjects, and individuals with high concentrations of this protein were more prone to type 2 diabetes development than those with low concentrations (28).

No daily changes in plasma adiponectin concentration were found by Hotta et al. (7) in obese non-diabetic and obese type 2 diabetic subjects. They also reported that the adiponectin plasma concentration correlated negatively with the fasting plasma insulin level and that it was not affected by food intake. In contrast, in a recent study, Gavrilova et al. (3) reported the presence of ultradian pulsatility of plasma adiponectin in healthy volunteers and a significant decline in this adipokine at night, followed by a nadir in the early morning.

In our study series, in which we studied the daily plasma adiponectin profiles in morbidly obese subjects before and after weight loss, we paradoxically found similarities to both of the above-cited studies (3,7). In the obese state both the frequency and amplitude of the 24-h adiponectin time series were very small, while in the postobese state both the pulsatility parameters increased significantly, becoming similar to those described by Gravilova et al. (3) in normal-weight healthy subjects. However, the nocturnal decline, starting in the late evening and continuing throughout the night to reach a nadir in the early morning, observed by Gravilova et al. (3) was not present in our data, although the same mathematical procedure was used. The authors suggest that cortisol may have an inhibitory effect on adiponectin secretion in normal subjects. However, in our series the cross-correlation analysis between long-term fluctuations of cortisol levels and adiponectin concentrations did not vary significantly before and after BPD, suggesting that, at least in morbidly obese subjects who underwent malabsorptive bariatric surgery with subsequent massive weight loss, cortisol is not the major determinant of increased adiponectin pulsatility. In contrast, insulin seems to correlate better with adiponectin pulsatility after (70%) than before (55%) BPD. After BPD, insulin peaked consistently before adiponectin, with an average lag period of 60 min, while the lag was negligible before BPD (2 min).

Therefore, this inconsistency might be ascribed to dysregulation of the hypothalamus-pituitary-adrenal (HPA) axis. The autonomic nervous system and HPA axis are reported as being over-activated in the morbidly obese state (29), while severely obese subjects, after massive weight reduction, seem to have reduced activation of counterregulatory hormones in response to induced hypoglycemia (30), accounting for the lack of any nocturnal decrease in adiponectin. Another possible explanation of this different nocturnal behavior of adiponectin circulating levels might be that, in spite of the massive weight loss, severe obese subjects maintain an imprinting, likely of genetic or epigenetic nature, of their former obese state, although the adiponectin pulsatility is restored during the daytime.

In our series, a significant correlation was found between adiponectin plasma levels and M value; as a result, the higher the adiponectin concentration, the higher the whole-body glucose uptake during the euglycemic clamp. It has been clearly demonstrated that adiponectin reduces TNF-α production and TNF-α–induced biological effects on cells (31–33). Hotta et al. (7) suggested that adiponectin may enhance insulin sensitivity by interfering with TNF-α production and signaling. Since we recently demonstrated that TNF-α mRNA expression is significantly reduced in skeletal muscle biopsies of severely obese subjects after BPD and correlates positively with increased insulin sensitivity (34), a mechanism of reciprocal inhibition of these two adipokines may be postulated.

Insulin suppresses adiponectin gene expression in both 3T3L1-cultured cell adipocytes and adipocytes isolated from human visceral adipose tissue (35). Thus, we can advance the hypothesis that the reversibility of hyperinsulinemia observed in the patients undergoing BPD may cause an increase in the synthesis of adiponectin in the adipocytes, as shown by the increased adiponectin plasma AUC. We believe that in the future, adiponectin plasma levels may come to be regarded as an indicator of the sensitivity of adipose tissue to insulin.

In conclusion, weight loss coupled with the reversibility of insulin resistance in formerly severely obese subjects restores homeostatic control of adiponectin secretion, thus contributing to a reduction of cardiovascular risk (31,36–39) in these patients.

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