0013-7227/01/$03.00/0
Printed in U.S.A.

The Journal of Clinical Endocrinology & Metabolism 86(8):3815–3819

Weight Reduction Increases Plasma Levels of an Adipose-Derived Anti-Inflammatory Protein, Adiponectin

WEI-SHIUNG YANG, WEI-JEI LEE, TOHRU FUNAHASHI, SACHIYO TANAKA, YUJI MATSUZAWA, CHIA-LING CHAO, CHI-LING CHEN, TONG-YUAN TAI, AND LEE-MING CHUANG

Department of Internal Medicine (W.-S.Y., C.-L.C., T.-Y.T., L.-M.C.), Graduate Institute of Clinical Medicine (W.-S.Y., L.-M.C.), College of Medicine, and Institute of Epidemiology (C.-L.C.), College of Public Health, National Taiwan University, Taipei 100; Department of Surgery (W.-J.L.), En Chu Kong Hospital, Taipei Hsien 237, Taiwan; and Department of Internal Medicine and Molecular Science (T.F., S.T., Y.M.), Graduate School of Medicine, Osaka University, 565-0871, Osaka, Japan

Adiponectin, an adipose tissue-specific plasma protein, was recently revealed to have anti-inflammatory effects on the cellular components of vascular wall. Its plasma levels were significantly lower in men than in women and lower in human subjects with obesity, type 2 diabetes mellitus, or coronary artery disease. Therefore, it may provide a biological link between obesity and obesity-related disorders such as atherosclerosis, against which it may confer protection. In this study, we observed the changes of plasma adiponectin levels with body weight reduction among 22 obese patients who received gastric partition surgery. A 46% increase of mean plasma adiponectin level was accompanied by a 21% reduction in mean body mass index. The change in plasma adiponectin levels was significantly correlated with the changes in body mass index ($r = -0.5$, $P = 0.01$), waist ($r = -0.4$, $P = 0.04$) and hip ($r = -0.6$, $P = 0.0007$) circumferences, and steady state plasma glucose levels ($r = -0.5$, $P = 0.04$). In multivariate linear regression models, the increase in adiponectin as a dependent variable was significantly related to the decrease in hip circumference ($\beta = -0.16$, $P = 0.028$), after adjusting body mass index and waist circumference. The change in steady state plasma glucose levels as a dependent variable was related to the increase of adiponectin with a marginal significance ($\beta = -0.92$, $P = 0.053$), after adjusting body mass index and waist and hip circumferences. In conclusion, body weight reduction increased the plasma levels of a protective adipocytokine, adiponectin. In addition, the increase in plasma adiponectin despite the reduction of the only tissue of its own synthesis suggests that the expression of adiponectin is under feedback inhibition in obesity. (*J Clin Endocrinol Metab* 86: 3815–3819, 2001)

OBESITY IS A pan-endemic health problem in both developed and developing countries. It increases risk for many common diseases, including coronary artery disease (CAD), type 2 diabetes mellitus (DM), hypertension, gallbladder disease, and osteoarthritis (1). Consequently, obesity increases total mortality (2, 3). Despite that its deleterious health effects are well recognized, how obesity is biologically linked to the pathogenesis of these disorders, especially atherosclerosis, remains obscure.

Adipose tissue, long being misconstrued as a mere tissue of fat storage, is now acknowledged to be an active participant in energy homeostasis and other physiological functions. The term "adipocytokines" was recently coined to describe the adipose-derived bioactive factors that modulate the physiological functions of the other tissues in our body (4, 5). Some well known examples among these factors include leptin, plasminogen activator inhibitor-1, and TNFα (6–8). It is highly possible that some of the adipocytokines may, in fact, mediate the systemic effects of obesity on health.

One of the most abundant adipose tissue-specific adipocytokines, adiponectin, was recently shown to modulate a wide array of biological functions (9, 10). Adiponectin has been shown to reduce TNFα-induced monocyte attachment to cultured human aortic endothelial cells by inhibiting the expression of vascular cell adhesion molecule, intercellular adhesion molecule, and E-selectin in endothelial cells (11). A cross-talk between adiponectin and TNFα-induced nuclear factor κB signaling may be mediated through cAMP-protein kinase A pathway (12). Furthermore, adiponectin was demonstrated to suppress phagocytic activity and lipopolysaccharide-induced TNFα production in cultured macrophages (13). It may also induce apoptosis of cells in myelomonogenic lineages (13). Taken together, these studies suggest that adiponectin may have anti-inflammatory effects, especially in endothelial cells and macrophages. In animal model, adiponectin was detected only in catheter-injured vessel wall, but not in intact vessels (14). The plasma levels of adiponectin were also demonstrated to be lower in men than in women and lower in subjects with obesity, CAD, and type 2 DM as well (11, 15, 16). For example, mean plasma adiponectin levels were 3.7 μg/ml and 8.9 μg/ml, respectively, for obese [mean body mass index (BMI), 31.9 kg/m^2] and nonobese (mean BMI, 22.8 kg/m^2) subjects in a previous study (15). These observations indicate that adiponectin may be a protective adipocytokine against atherosclerosis. Therefore, any measure that could be taken to increase adiponectin may be beneficial.

Expression of adipoQ, the mouse homologue of adiponectin, was detectable by Northern blot on d 4 during the differentiation of 3T3-L1 fibroblasts into adipocytes (17). We have also shown that the steady state mRNA of adipoQ was increased in 3T3-L1 adipocytes after 24-h treatment of a per-

Abbreviations: AUC, Area under curve; BMI, body mass index; CAD, coronary artery disease; DM, diabetes mellitus; HOMA, homeostasis model assessment; OGTT, oral glucose tolerance test; SSPG, steady state plasma glucose.

oxisome proliferator-activated receptor γ agonist, rosiglitazone (18). However, plasma adiponectin levels were found to be lower in obese human subjects (15). In ob/ob mice, the steady state mRNA of adipoQ was found to be down-regulated as well (17). It is plausible that the expression of adiponectin is activated during adipogenesis, but a feedback inhibition on its production may be imposed in the development of obesity. In fact, the expression of adipogenic genes was recently reported to decrease in the development of obesity in mice (19).

In this study, we have intended to observe the changes of plasma adiponectin levels with body weight loss in obese patients who received gastric partition surgery (20). First, we argued that a significant increase of this anti-inflammatory protein might at least partially explain the beneficial effects of weight reduction (21, 22). Second, we argued that if adiponectin were under feedback inhibition in obesity, body weight loss would also result in an increase of its plasma levels, despite losing the tissue of synthesis.

Subjects and Methods

Subjects

Twenty-two severely obese patients (age, 34.0 ± 11.4 yr old; 15 females and 7 males) who met the criteria for surgery according to the NIH consensus were recruited for this study (23). All patients were evaluated with series of physical examination and routine tests for hematology, biochemistry, electrolytes, cardiopulmonary functions, and endocrine functions (including thyroid-stimulating hormone, T_4), and plasma glucose concentrations. Gastric partition surgery was performed at En-Chu-Kong Hospital, Taipei Hsien, as described previously (20). Written informed consent was obtained from each individual, and the study was reviewed and approved by the Institutional Review Board.

Biochemical measurements

A 75-g oral glucose tolerance test (OGTT) and an insulin suppression test were given to all subjects before and 3–12 months after the surgery on two separate days after overnight fasting. The insulin suppression test was used to assess insulin-mediated glucose disposal as reflected by the steady state plasma glucose (SSPG) as described previously (24). The concentrations of plasma glucose, total cholesterol, and triglyceride were measured in fasting samples by an autoanalyzer (Hitachi 7250 special; Hitachi, Tokyo, Japan). Serum insulin levels were determined by a microparticle enzyme immunoassay using AxSYM system from Abbott Diagnostics (Abbott Laboratories, Dainabot Co. Ltd., Tokyo, Japan). The homeostasis model assessment is applied to estimate the degree of insulin resistance [HOMA IR = Insulin/$22.5e^{-\text{In(Glucose)}}$] and β cell function [HOMA β = 20× Insulin/(Glucose - 3.5)], where insulin in pmol/liter and glucose in mM (25). Plasma levels of adiponectin were determined by an ELISA system as described (15). All the measurements, except those of adiponectin, were presented in System International units because the molecular weight of adiponectin has not been precisely determined.

Statistical analyses

Data were presented in means and SD. Statistical analyses including paired *t* test, correlation analysis, and multivariate linear regression analysis were performed by using the PC version of the Statistical Analysis System (6.12 edition; SAS Institute, Inc., Cary, NC). Differences in selected clinical characteristics between those before and after the gastric partition surgery were tested by paired *t* test. Correlation matrix of all the changes in clinical characteristics and changes in plasma adiponectin levels before and after the surgery was performed. Several multivariate linear regression models were performed that included age, gender, changes in plasma adiponectin levels, BMI, waist circumference, and hip circumference as independent variables; and changes in plasma adiponectin levels and SSPG as dependent variables, respectively.

Results

Twenty-two obese patients received gastric partition surgery and were followed for a mean of 7.7 (±3.5) months. The

TABLE 1. Mean and SD of selected characteristics before and after gastric partition surgery in 22 obese patients

Variables	No.	Before surgery		After surgery		P[α]
		Mean	SD	Mean	SD	
Weight (kg)	22	107.6	21.7	84.3	16.5	0.0000
BMI (kg/m^2)	22	39.57	5.89	31.22	5.21	0.0000
Waist (cm)	22	116.1	16.6	96.7	14.0	0.0000
Hip (cm)	22	121.9	11.6	108.0	11.2	0.0000
WHR	22	0.34	0.02	0.32	0.02	0.0002
DBP (mm Hg)	21	70	11	68	11	0.42
SBP (mm Hg)	21	124	20	114	16	0.026
Adiponectin (μg/mliter)	22	4.53	1.46	6.63	2.32	0.0000
FPG (mmol/liter)	21	6.46	1.20	5.36	0.65	0.0009
2h-PG (mmol/liter)	18	8.95	2.28	5.89	1.90	0.0000
AUCg (mmol h/liter)	18	19.74	3.97	16.05	4.13	0.0004
FPI (pmol/liter)	22	186.6	82.5	66.7	45.9	0.0000
2h-PI (pmol/liter)	18	742.6	408.3	562.5	710.3	0.22
AUCi (pmol h/liter)	18	1856.9	1069.8	1965.2	1171.0	0.73
IR (by HOMA)	21	10.5	6.6	3.2	2.1	0.0000
IS (by HOMA)	21	264.9	144.2	171.1	153.1	0.010
SSPG (mmol/liter)	21	15.98	2.72	3.34	3.61	0.050
SSPI (pmol/liter)	22	498.6	278.3	368.4	148.7	0.027
T-chol (mmol/liter)	22	4.10	0.86	4.28	0.89	0.34
TG (mmol/liter)	22	1.69	0.98	0.99	0.36	0.0004
HDL-C (mmol/liter)	22	1.20	0.33	1.10	0.31	0.084
HDL-C/T-chol	22	0.31	0.14	0.26	0.09	0.12

WHR, Waist to hip ratio; DBP, diastolic blood pressure; SBP, systolic blood pressure; FPG, fasting plasma glucose; 2h-PG, 2-h plasma glucose; AUCg, AUC of plasma glucose; FPI, fasting plasma insulin; 2h-PI, 2-h plasma insulin; AUCi, AUC of plasma insulin; IR, insulin resistance index; IS, insulin secretion index.

[α] Paired *t* test.

changes of selected characteristics in these patients are shown in Table 1. Reductions in body weight, BMI, waist circumference, hip circumference, and waist to hip ratio were 23.3 kg (±11.5), 8.35 kg/m^2 (±3.8), 19.5 cm (±13.0), 13.9 cm (±7.6), and 0.02 (±0.02), respectively. The differences between the means of these variables before and after surgery were highly significant.

The changes in fasting (1.09 ± 1.28 mmol/liter) and 2-h postglucose load (3.05 ± 2.02 mmol/liter) plasma glucose levels as well as the area under curve (AUC) (3.75 ± 3.60 mmol h/liter) of plasma glucose during an OGTT were significantly reduced after gastric partition surgery, suggesting a beneficial effect of body weight loss on carbohydrate metabolism (Table 1). Mean fasting plasma insulin level (119.8 ± 80.4 pmol/liter) was significantly reduced, whereas the changes of 2-h postglucose load plasma insulin and AUC of plasma insulin were not statistically significant. In fact, the AUC of plasma insulin slightly increased with body weight loss, mainly due to the elevated insulin levels at 1 h during an OGTT. This indicates that insulin secretion in response to glucose stimulation was not impaired with weight reduction. On the other hand, the significant decrease both in insulin resistance index (7.46 ± 6.53) by HOMA and in SSPG (1.54 ± 3.38 mmol/liter) was consistent with increased insulin sensitivity with weight reduction among these obese subjects. Significant changes with weight loss among the other variables included reduction in plasma triglyceride levels and systolic blood pressure.

Along with all the changes described above, plasma levels of adiponectin were increased by a mean of 2.1 (±1.8) μg/ml (46% of the mean presurgical level) with a 21% reduction in BMI (Table 1). The change in plasma levels of adiponectin was significantly correlated with those of BMI ($\gamma = -0.5$, $P = 0.01$), waist circumference ($\gamma = -0.4$, $P = 0.04$), hip circumference ($\gamma = -0.6$, $P = 0.0007$), and SSPG ($\gamma = -0.5$, $P = 0.04$) (Fig. 1). In a multivariate linear regression model, the change of plasma adiponectin levels as a dependent variable was significantly related to hip circumference only, while adjusting age, sex, changes in BMI, and waist circumference (Table 2). Before adjusting changes in waist and hip circumferences, the change in BMI was also significantly related to that of plasma adiponectin (data not shown). On the other hand, the change in SSPG as the dependent variable was related to the change of plasma adiponectin with a marginal statistical significance, while adjusting age, sex, and changes in BMI, and waist and hip circumferences (Table 2).

Discussion

Adiponectin is an adipose tissue-specific plasma protein. It was recently demonstrated to modulate a variety of biological functions (11–13). It decreased TNFα-induced mac-

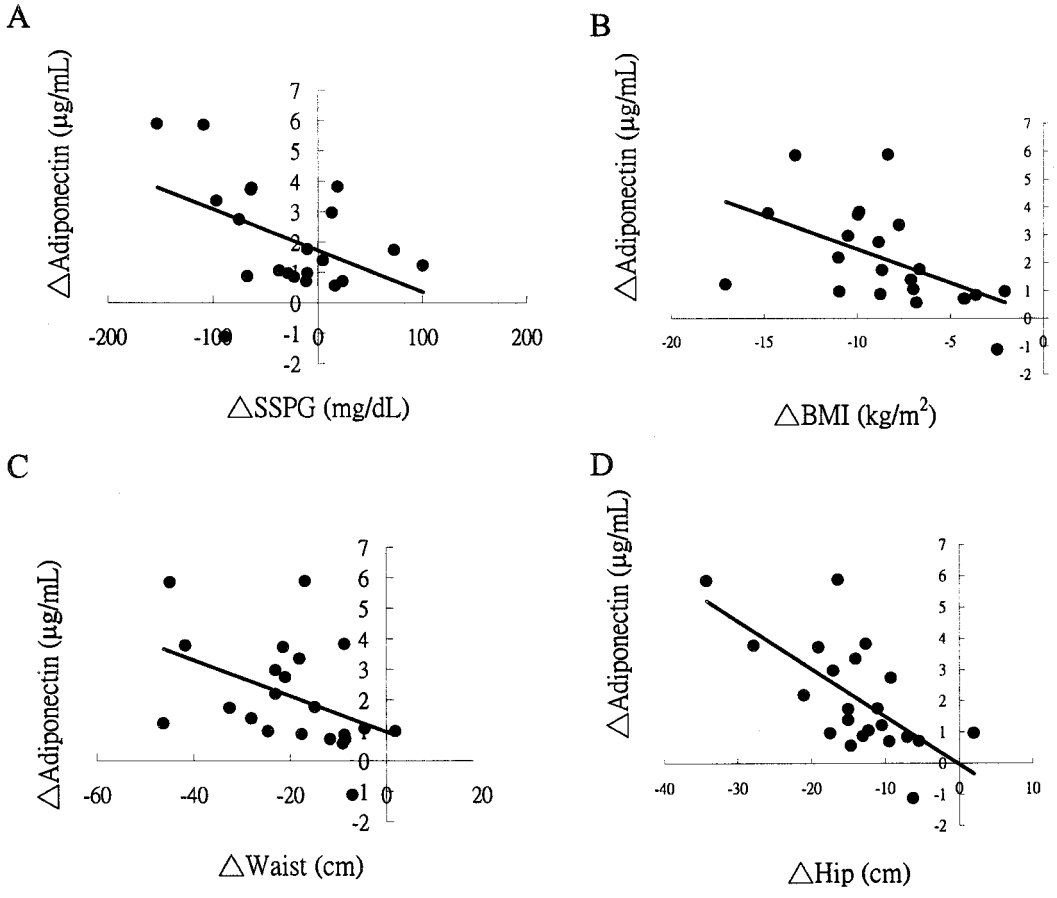

FIG. 1. The change (Δ) of plasma adiponectin levels before and after gastric partition surgery plotted against the changes (Δ) in SSPG (A), BMI (B), waist circumference (C), and hip circumference (D) in 22 subjects.

TABLE 2. Multivariate linear models showing regression coefficients ± SE of changes (Δ) of plasma adiponectin levels and SSPG as dependent variables with age, gender, and changes in plasma adiponectin, BMI, waist circumference (W), and hip circumference (H) as independent variables in a group of 22 subjects

Dependent variables	ΔAdiponectin	ΔSSPG			
	Model I	Model I	Model II	Model III	Model IV
Independent variables					
Intercepts	−1.06 ± 1.56	2.96 ± 2.51	−0.32 ± 2.33	−0.02 ± 2.56	1.58 ± 2.69
Age (yr)	0.01 ± 0.03	−.008 ± 0.06	−0.05 ± 0.005	−0.06 ± 0.05	−0.08 ± 0.05
Sex	−0.05 ± 0.75	−2.13 ± 1.49	−3.34 ± 1.29	−3.39 ± 1.33	−2.84 ± 1.35
ΔAdiponectin (μg/ml)		−0.77 ± 0.40[b]	−1.28 ± 0.37[c]	−1.28 ± 0.38[e]	−0.92 ± 0.44[f]
ΔBMI (kg/m^2)	−1.69 ± 0.17		−0.54 ± 0.18[d]	−0.46 ± 0.32	−0.43 ± 0.31
ΔW (cm)	0.05 ± 0.52			−0.03 ± 0.09	−0.09 ± 0.09
ΔH (cm)	−0.16 ± 0.07[a]				0.21 ± 0.14

[a] $P = 0.028$; [b] $P = 0.07$; [c] $P = 0.003$; [d] $P = 0.008$; [e] $P = 0.0042$; [f] $P = 0.053$; regression coefficients significantly different from 0.

rophage attachment to endothelial cells by reducing the expression of adhesion molecules in endothelial cells through protein kinase A-mediated interference of nuclear factor κB signaling (11, 12). It was also shown to suppress TNFα production and phagocytic activity in macrophages (13). These indicate that adiponectin has anti-inflammatory properties. In addition, adiponectin was detectable in catheter-injured vessel wall, rather than in intact vessels in animal models (14). This suggests that it may participate in the pathogenesis of atherosclerosis. In fact, it was documented that lower levels of plasma adiponectin was associated with CAD and risk factors of CAD, including male sex, obesity, and type 2 DM (11, 15, 16). Therefore, adiponectin provides a direct biological link between obesity and atherosclerosis. Body weight loss, a common medical practice to reduce the risk of CAD, type 2 DM, and hypertension, would be expected to increase plasma adiponectin levels, if it were to mediate the beneficial effects of weight reduction. In this study, we demonstrated that this was indeed the case.

Recently, it was demonstrated that iv injection of the C-terminus globular domain of the mouse homologue of adiponectin reduced plasma fatty acid levels and diet-induced weight gain in mice (26). This indicates that adiponectin may participate in fatty acid and energy homeostasis. We observed a significant decrease in triglyceride levels after weight reduction in this study. Whether this is in part caused by altered fatty acid metabolism secondary to the increase in plasma adiponectin remains unknown. We did not assay plasma fatty acid levels in this study.

In obesity, plasma adiponectin levels were lower despite that adipose tissue is the only tissue of its synthesis, suggesting a negative feedback on its production. Consequently, body weight reduction would result in at least transient disinhibition, therefore, an elevation of plasma adiponectin. Recent demonstration by microarray that the expression of adipogenic genes was suppressed in the development of obesity and DM in mice argues for the existence of a feedback inhibitory pathway (19). In addition, the expression of adipoQ, the mouse homologue of adiponectin, and adiponectin was down-regulated, respectively, in ob/ob obese mice and in obese human subjects (17). This is also consistent with the existence of a negative feedback pathway.

The mechanisms of regulating plasma adiponectin levels by body weight change are still not known. The fact that the steady state mRNA of adipoQ (the mouse homologue of adiponectin) decreased in ob/ob mice compared with those of wild type indicates that the level of regulation is, in part, at transcription or mRNA stability (17). It was also shown that the steady state mRNA of adiponectin in adipose tissue seems to be reduced in obese human subjects (17). Because the weight reduction in this study was accomplished by gastric partition surgery, it is highly possible that some neuro-hormonal factors, especially gut peptides like gastrin, cholecystokinin, and so on, may be involved in regulating the expression of adiponectin expression. Exactly what biological signals that modulate the expression of adiponectin during weight reduction merit further studies. So far, the only hormone known to regulate adiponectin expression is insulin (27).

In this study, we also showed that elevation of plasma adiponectin levels was correlated with the change in SSPG. In multivariate linear regression model, the change of plasma adiponectin was related to the change in SSPG with a marginal statistical significance, after those of BMI and waist and hip circumferences were adjusted. This implies that adiponectin may have a direct effect on insulin sensitivity or vice versa. Adiponectin was clearly demonstrated to reduce TNFα production and TNFα-induced biological effects on certain cells. Therefore, it is highly plausible that it may enhance insulin sensitivity by interfering with TNFα production and signaling. This awaits further investigation.

In conclusion, we have convincingly showed that body weight reduction increased plasma adiponectin levels. This provides a novel biological explanation for the beneficial effect of body weight loss on reducing cardiovascular risk in obese patients. The result is also compatible with the speculation that adiponectin might be under a strict feedback regulation by body fat mass.

Acknowledgments

Received February 12, 2001. Accepted April 27, 2001.

Address all correspondence and requests for reprints to: Lee-Ming Chuang, M.D., Ph.D., Department of Internal Medicine, National Taiwan University Hospital, 7 Chung-Shan South Road, Taipei 100, Taiwan. E-mail: leeming@ha.mc.ntu.edu.tw.

This work was supported by Program for Promoting Academic Excellence of Universities (89-B-FA01-1-4) from the Department of Education and a grant from the National Science Council (NSC89-2314-B-002-065) of the Republic of China.

References

1. **Must A, Spadano J, Coakley EH, Field AE, Colditz G, Dietz WH** 1999 The disease burden associated with overweight and obesity. JAMA 282:1523–1529
2. **Allison DB, Fontaine KR, Manson JE, Stevens J, VanItallie TB** 1999 Annual deaths attributable to obesity in the United States. JAMA 284:1530–1538
3. **Calle EE, Thun MJ, Petrelli JM, Rodriguez C, Heath Jr CW** 1999 Body-mass index and mortality in a prospective cohort of U.S. adults. N Engl J Med 341:1097–1105
4. **Matsuzawa Y, Funahashi T, Nakamura T** 1999 Molecular mechanism of metabolic syndrome X: contribution of adipocytokines adipocyte-derived bioactive substances. Ann NY Acad Sci 892:146–154
5. **Funahashi T, Nakamura T, Shimomura I, et al.** 1999 Role of adipocytokines on the pathogenesis of atherosclerosis in visceral obesity. Intern Med 38: 202–206
6. **Ozata M, Ozdemir IC, Licinio J** 1999 Human leptin deficiency caused by a missense mutation: multiple endocrine defects, decreased sympathetic tone, and immune system dysfunction indicate new targets for leptin action, greater central than peripheral resistance to the effects of leptin, and spontaneous correction of leptin-mediated defects. J Clin Endocrinol Metab 84:3686–3695 (erratum in J Clin Endocrinol Metab 2000, 85:416)
7. **Shimomura I, Funahashi T, Takahashi M, et al.** 1996 Enhanced expression of PAI-1 in visceral fat: possible contributor to vascular disease in obesity. Nat Med 2:800–803
8. **Hotamisligil GS, Shargill NS, Spiegelman BM** 1993 Adipose expression of tumor necrosis factor-α: direct role in obesity-linked insulin resistance. Science 259:87–91
9. **Maeda K, Okubo K, Shimomura I, Funahashi T, Matsuzawa Y, Matsubara K** 1996 cDNA cloning and expression of a novel adipose specific collagen-like factor, apM1. Biochem Biophys Res Commun 221:286–289
10. **Nakano Y, Tobe T, Choi-Miura NH, Mazda T, Tomita M** 1996 Isolation and characterization of GBP28, a novel gelatin-binding protein purified from human plasma. J Biochem 120:803–812
11. **Ouchi N, Kihara S, Arita Y** 1999 Novel modulator for endothelial adhesion molecules: adipocyte-derived plasma protein adiponectin. Circulation 100: 2473–2476
12. **Ouchi N, Kihara S, Arita Y, et al.** 2000 Adiponectin, an adipocyte-derived plasma protein, inhibits endothelial NF-κB signaling through a cAMP-dependent pathway. Circulation 102:1296–1301
13. **Yokota T, Oritani K, Takahashi I, et al.** 2000 Adiponectin, a new member of the family of soluble defense collagens, negatively regulates the growth of myelomonocytic progenitors and the functions of macrophages. Blood 96: 1723–1732
14. **Okamoto Y, Arita Y, Nishida M, et al.** 2000 An adipocyte-derived plasma protein, adiponectin, adheres to injured vascular walls. Horm Metab Res 32:47–55
15. **Arita Y, Kihara S, Ouchi N, et al.** 1999 Paradoxical decrease of an adipose-specific protein, adiponectin, in obesity. Biochem Biophys Res Commun 257: 79–83
16. **Hotta K, Funahashi T, Arita Y, et al.** 2000 Plasma concentrations of a novel, adipose-specific protein, adiponectin, in type 2 diabetic patients. Arterioscler Thromb Vasc Biol 20:1595–1599
17. **Hu E, Liang P, Spiegelman BM** 1996 AdipoQ is a novel adipocyte-specific gene dysregulated in obesity. J Biol Chem. 271:10697–10703
18. **Lin WS, Chang HM, Tai TY, Chuang LM** 1999 Effect of thiazolidinedione on gene expression in NIH3T3–L1 adipocytes. Diabetes 48(Suppl 1):A217
19. **Nadler ST, Stoehr JP, Schueler KL, Tanimoto G, Yandell BS, Attie AD** 2000 The expression of adipogenic genes is decreased in obesity and diabetes mellitus. Proc Natl Acad Sci USA 97:11371–11376
20. **Chen KM, Lee WJ, Lai HS, Chen WJ** 1998 Fifteen years' experience with gastric partitioning for obesity treatment. J Formos Med Assoc 97:381–386
21. **Williamson DF, Thompson TJ, Thun M, Flanders D, Pamuk E, Byers T** 2000 Intentional weight loss and mortality among overweight individuals with diabetes. Diabetes Care 23:1499–1504
22. **Heymsfield SB, Segal KR, Hauptman J, et al.** 2000 Effects of weight loss with orlistat on glucose tolerance and progression to type 2 diabetes in obese adults. Arch Intern Med 160:1321–1326
23. **Consensus Development Conference Statement** 1991 Gastrointestinal surgery for severe obesity. Ann Intern Med 115:956
24. **Pei D, Jones CN, Bhargava R, Chen YD, Reaven GM** 1994 Evaluation of octreotide to assess insulin-mediated glucose disposal by the insulin suppression test. Diabetologia 37:843–845
25. **Mattews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC** 1985 Homeostasis model assessment: insulin resistance and β-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 28:412–419
26. **Fruebis J, Tsao TS, Javorschi S, et al.** 2001 Proteolytic cleavage product of 30 Kd adipocyte complement-related protein increases fatty acid oxidation in muscle and causes weight loss in mice. Proc Natl Acad Sci USA 98:2005–2010
27. **Scherer PE, Williams S, Fogliano M, Baldini G, Lodish HF** 1995 A novel serum protein similar to C1q, produced exclusively in adipocytes. J Biol Chem 270:26746–26749