Adiponectin as an Independent Predictor of the Presence and Degree of Hepatic Steatosis in the Dallas Heart Study

Aslan T. Turer, Jeffrey D. Browning, Colby R. Ayers, Sandeep R. Das, Amit Khera, Gloria L. Vega, Scott M. Grundy, and Philipp E. Scherer

Department of Medicine (A.T.T., S.R.D., A.K.), Division of Cardiology; Advanced Imaging Research Center (J.D.B.); Department of Medicine (J.D.B.), Division of General Internal Medicine; Donald W. Reynolds Cardiovascular Clinical Research Center (C.R.A., S.R.D., A.K.); Center for Human Nutrition (G.L.V., S.M.G.); Department of Medicine (P.E.S.), Touchstone Diabetes Center; and Department of Cell Biology (P.E.S.), University of Texas Southwestern Medical Center, Dallas, Texas 75390

Context: Previous small case-control studies have suggested an inverse relationship between adiponectin and hepatic steatosis, but whether this finding is independent of insulin sensitivity and other intraabdominal fat depots is unclear.

Objectives and Main Outcome Measures: The objective of this study was to establish whether an independent relationship exists between serum adiponectin concentrations and liver fat.

Design, Setting, and Patients: Adiponectin levels were compared with hepatic triglyceride content (HTGC) as assessed by proton magnetic resonance spectroscopy in 2215 participants from the Dallas Heart Study. Multivariate modeling was performed to control for the effects of intraabdominal fat, insulin sensitivity, and other baseline factors.

Results: In unadjusted analysis, adiponectin levels displayed inverse correlations with the amount of intraabdominal fat and HTGC. After multivariate adjustment, including individual intraabdominal fat depots and homeostasis model assessment of insulin resistance, HTGC remained significantly associated with adiponectin levels ($\beta = -1.46$, $P < 0.0001$ for women; $\beta = -1.81$, $P < 0.0001$ for men). Race- and gender-specific models demonstrated that this association was consistent across groups, except for Hispanic men. The adjusted odds ratio for hepatic steatosis (HTGC > 5.5%) per 1-SD increase in adiponectin concentrations was 0.64 (95% confidence interval = 0.52–0.78) for women and 0.61 (95% confidence interval = 0.51–0.74) for men.

Conclusion: Data from a large, multiethnic population-based cohort show adiponectin levels are inversely associated with hepatic steatosis even after controlling for measures of insulin sensitivity, extrahepatic abdominal adiposity, and ethnicity. The mechanistic underpinnings of this association warrant further exploration. **(*J Clin Endocrinol Metab* 97: E982–E986, 2012)**

A major sequela of obesity and insulin resistance is nonalcoholic fatty liver disease (NAFLD). Currently, NAFLD afflicts one quarter to one third of adults in Western societies (1, 2) and is responsible for 20% of newly diagnosed cases of chronic liver disease (3). This number is only anticipated to rise with the increasing prevalence of obesity and insulin resistance.

The ectopic deposition of triglycerides in liver is fundamental in the pathogenesis of NAFLD. Recent work indicates that the majority of triglycerides (TG) in the fatty liver are lipolytic in origin (4). This has led to the notion that adipose tissue may play a key role in the initiation and progression of this disease.

Adiponectin is an adipokine constitutively expressed by adipose tissue, but its circulating levels are inversely proportional to measures of adiposity. Adiponectin has well-described antiinflammatory (5) and insulin-sensitiz-

ISSN Print 0021-972X ISSN Online 1945-7197
Printed in U.S.A.

doi: 10.1210/jc.2011-3305 Received December 6, 2011. Accepted February 23, 2012.
First Published Online March 21, 2012

Abbreviations: CI, Confidence interval; DHS, Dallas Heart Study; HFD, high-fat diet; HOMA-IR, homeostasis model assessment of insulin resistance; HTGC, hepatic TG content; ^{1}H-MRS, proton magnetic resonance spectroscopy; MRI, magnetic resonance imaging; NAFLD, nonalcoholic fatty liver disease; TG, triglyceride.

ing properties (6–8) and appears to play a causal role in the development of steatosis in animal models (9). Previous human association studies of adiponectin and liver fat have been performed but have been limited by small sample size, referral bias, and inability to adequately control for significant confounders (10). To elucidate the relationship between adiponectin and liver fat, and to address the shortcomings of previous studies, we examined the association of adiponectin and hepatic TG content (HTGC) using proton magnetic resonance spectroscopy (^{1}H-MRS) from a large population-based cohort study of Dallas County residents ages 30–65 yr.

Subjects and Methods

Study population

The details of the design of the Dallas Heart Study (DHS) have been described previously (11). In brief, the DHS is a multiethnic population-based probability sample of Dallas County residents aged 18–65 yr, with an intentional oversampling of African-Americans to comprise half the study cohort. The study population was comprised of the 2215 subjects at least 30 yr old who were self-identified as Black, Hispanic, or White and completed all three phases of data collection [inclusive of magnetic resonance imaging (MRI) and spectroscopy].

Blood samples

Participants underwent phlebotomy after an overnight fast during a second home visit. A total of 40 ml blood was collected in tubes containing a serum separator or citrate-EDTA and maintained at 4 C for less than 4 h before processing. The tubes were centrifuged (1000 × *g* for 15 min at 4 C), and plasma was isolated.

Abdominal fat quantification

Participants were scanned on a 1.5-Tesla MRI (INTERA; Philips Medical Systems, Best, The Netherlands). The abdomen was scanned from the diaphragm to the pelvis using contiguous 10-mm axial slices. The total abdominal adipose tissue was partitioned into individual components of ip, retroperitoneal, and sc compartments using manually circumscribed contours on a single slice taken at the L2–L3 level. These derived areas were used to determine fat mass in kilograms using previously determined regression equations (12).

^{1}H-MRS for hepatic triglyceride

At the time of abdominal fat quantification, subjects also underwent determination of HTGC, as previously described (13). Briefly, after planning images were obtained, a 27-cm^3 volume of interest was selected in the right hepatic lobe, avoiding major blood vessels, bile ducts, and the lateral margins of the liver. Spectra were obtained using a point-resolved spectroscopy sequence and the Q-body coil for radiofrequency-transmission and reception. Peak areas under the methylene (1.4 ppm) and water (4.8 ppm) signals were determined using commercially available software (NUTS; Acorn NMR, Fremont, CA) and used to calculate HTGC, expressed as a percentage of fat-to-total signals [*i.e.* fat/(fat + water)]. The presence of hepatic steatosis was defined as a HTGC higher than 5.5%, as previously determined for a low-risk population from this study cohort (13).

Adiponectin measurements

Blood samples were collected in EDTA-containing tubes after an overnight fast. Plasma aliquots were stored at −80 C until assays were performed. Total circulating adiponectin levels were quantified using a commercially available sandwich ELISA (Millipore, Billerica, MA), according to the manufacturer's protocols.

Statistical analysis

The clinical, anthropomorphic, and biochemical data of the study population are reported as proportions or median values with 25th and 75th percentiles, as appropriate. Adiponectin levels were modeled following a natural logarithm transformation. Univariate correlations were expressed using the Pearson correlation coefficient (r) except in the case of liver fat, which was, owing to its nonparametric distribution, expressed using the Spearman correlation coefficient (r_s). Multivariable logistic and linear regression models were generated to test the association between log adiponectin and both the presence and degree of hepatic steatosis, respectively. Models were adjusted for age, race, height, hypertension, diabetes, homeostasis model assessment of insulin resistance (HOMA-IR), triglycerides, low-density lipoprotein, high-density lipoprotein, alcohol use (grams per week), and MRI measures of intraabdominal adiposity (sc, ip, and retroperitoneal fat). Because of the significant gender difference in anthropometric features and adiponectin levels, separate sets of models were generated for males and females. P values <0.05 were considered statistically significant. All analyses were performed using SAS version 9.2 (SAS Corp., Cary, NC).

Results

Clinical and body composition features of the study population

Baseline clinical, biochemical, and anthropomorphic characteristics of the study population, stratified by race and gender, are shown in Table 1. The relationship between adiponectin and HTGC is shown in Supplemental Fig. 1.

Correlations between intraabdominal adiposity and adiponectin levels

As shown in Table 2, adiponectin levels displayed significant inverse correlation with the amount of intraabdominal fat and HTGC for each gender/ethnic subgroup, although these relationships were attenuated for the abdominal fat measures among Hispanic men. After multivariate adjustment for each independent measure of intraabdominal fat mass, HTGC remained significantly associated with adiponectin levels. Race- and gender-spe-

TABLE 1. Baseline demographic, biochemical, and anthropomorphic features of the DHS study cohort

		Women (n = 1182)			Men (n = 1033)		
	All (n = 2215)	Black (n = 600)	Hispanic (n = 225)	White (n = 357)	Black (n = 490)	Hispanic (n = 170)	White (n = 373)
Age (yr)	44 (37–53)	46 (37–54)	38 (34–48)	48 (39–55)	45 (38–54)	40 (33–47)	44 (38–52)
Hypertension [n (%)]	738 (34)	276 (47)	35 (16)	89 (25)	214 (44)	28 (17)	96 (26)
Hyperlipidemia [n (%)]	295 (13)	82 (14)	19 (8)	46 (13)	80 (16)	13 (8)	55 (15)
Diabetes mellitus [n (%)]	239 (11)	80 (13)	26 (12)	16 (4)	70 (14)	24 (14)	23 (6)
Current smoking [n (%)]	618 (28)	158 (26)	28 (12)	91 (26)	188 (39)	50 (29)	103 (28)
Alcohol use [n (%)]	1552 (70)	344 (58)	118 (52)	292 (82)	363 (74)	129 (76)	306 (82)
LDL (mg/dl)	106 (82–128)	107 (82–129)	99 (81–121)	104 (82–124)	102 (79–126)	112 (88–134)	111 (90–134)
HDL (mg/dl)	48 (40–57)	51 (44–63)	48 (40–55)	53 (44–63)	48 (40–57)	40 (35–49)	41 (35–47)
TG (mg/dl)	97 (68–147)	81 (61–115.5)	110 (79, 157)	98 (70–144)	90 (64–132)	131 (84–213)	121 (81–187)
HOMA-IR	2.9 (1.6–4.9)	3.6 (2.0–5.4)	3.3 (1.8–5.6)	2.1 (1.3–3.5)	2.9 (1.5–5.2)	3.3 (1.8–4.9)	2.5 (1.4–4.2)
Adiponectin (μg/ml)	6.7 (4.5–9.7)	6.4 (4.5–9.3)	7.7 (5.0–10.0)	10.5 (7.7–14.0)	5.0 (3.4–7.4)	5.7 (3.8–7.8)	6.4 (4.6–9.2)
BMI (kg/m^2)	29.0 (25.2–33.7)	31.4 (27.1–37.4)	30.1 (26.2–34.1)	26.6 (23.4–32.3)	28.4 (24.5–33.0)	29.2 (26.0–31.8)	28.4 (25.2–31.3)
Total abdominal fat (kg)	6.6 (4.8–8.7)	7.7 (5.4–10.6)	7.1 (5.6–9.2)	6.1 (4.4–8.5)	5.5 (3.8–7.7)	5.9 (4.9–7.4)	6.5 (5.0–8.1)
SC abdominal fat (kg)	4.2 (2.8–6.1)	5.8 (4.0–8.1)	5.1 (3.8–7.0)	4.4 (2.9–6.3)	3.2 (2.0–4.8)	3.2 (2.5–4.0)	3.6 (2.6–4.6)
IP fat (kg)	1.3 (0.9–1.8)	1.1 (0.8–1.5)	1.2 (0.9–1.6)	1.1 (0.7–1.5)	1.4 (0.9–1.8)	1.7 (1.3–2.1)	1.7 (1.2–2.2)
RP fat (kg)	0.8 (0.6–1.0)	0.6 (0.5, 0.8)	0.7 (0.6–0.9)	0.6 (0.5–0.9)	0.9 (0.6–1.1)	1.1 (0.8–1.3)	1.1 (0.8–1.3)
HTGC (%)	3.6 (2.1–6.5)	3.3 (2.0–5.4)	4.6 (2.6–9.9)	3.0 (1.8–5.3)	3.2 (2.0–5.21)	4.7 (2.7–11.9)	4.4 (2.4–8.6)
Hepatic steatosis [n (%)]	680 (31)	146 (24)	101 (45)	84 (24)	113 (23)	79 (46)	157 (42)

Categorical variables are presented as total number and proportion. Continuous variables are presented as median (25–75th percentile). For conversion TG, LDL, and HDL (milligrams per deciliter), multiply by 0.02586 for millimoles per liter. BMI, Body mass index; HDL, high-density lipoprotein; LDL, low-density lipoprotein; RP, retroperitoneal.

cific models demonstrated that this association was consistent across groups, except for Hispanic men.

Predictors of hepatic steatosis

In unadjusted logistic regression analysis, adiponectin concentrations were significantly associated with the presence of hepatic steatosis, with an odds ratio (per 1-SD increase in adiponectin concentrations) of 0.54 [95% confidence interval (CI) = 0.47–0.62] for women and 0.58 (95% CI = 0.51–0.67) for men. Even after controlling for several pertinent clinical features and MRI measures of abdominal adiposity (ip, retroperitoneal, and sc fat), adiponectin concentrations were significantly associated with the presence of steatosis, with an odds ratio of 0.64 (95% CI = 0.52–0.78) for women and 0.61 (95% CI = 0.51–0.74) for men.

Discussion

The present study determined the relationship between plasma adiponectin and hepatic TG content in a large,

TABLE 2. Univariate and multivariate correlations between MRI-determined body composition parameters and (log) adiponectin concentrations stratified by race/ethnicity and gender

	Women				Men			
	Black (n = 600)	Hispanic (n = 225)	White (n = 357)	All women (n = 1182)	Black (n = 490)	Hispanic (n = 170)	White (n = 373)	All men (n = 1033)
Univariate correlations (r, *P* value)								
Total abdominal fat	−0.32, <0.0001	−0.19, 0.002	−0.31, <0.0001	−0.33, <0.0001	−0.27, <0.0001	−0.12, 0.090	−0.34, <0.0001	−0.24, <0.0001
SC abdominal fat	−0.29, <0.0001	−0.14, 0.024	−0.29, <0.0001	−0.31, <0.0001	−0.21, <0.0001	−0.06, 0.440	−0.28, <0.0001	−0.20, <0.0001
IP fat	−0.33, <0.0001	−0.26, <0.0001	−0.30, <0.0001	−0.29, <0.0001	−0.31, <0.0001	−0.14, 0.044	−0.32, <0.0001	−0.23, <0.0001
RP fat	−0.32, <0.0001	−0.32, <0.0001	−0.29, <0.0001	−0.28, <0.0001	−0.30, <0.0001	−0.23, 0.001	−0.30, <0.0001	−0.22, <0.0001
HTGC	−0.33, <0.0001	−0.34, <0.0001	−0.34, <0.0001	−0.33, <0.0001	−0.35, <0.0001	−0.32, <0.0001	−0.42, <0.0001	−0.33, <0.0001
Multivariate correlations (β, *P* value)								
SC abdominal fat	0.003, 0.701	0.024, 0.091	−0.007, 0.552	0.004, 0.515	0.021, 0.113	0.092, 0.007	−0.006, 0.675	0.012, 0.205
IP fat	−0.137, 0.002	0.091, 0.380	0.002, 0.975	−0.094, 0.002	−0.121, 0.001	0.101, 0.340	0.074, 0.160	−0.086, 0.005
RP fat	−0.130, 0.015	−0.365, 0.034	−0.069, 0.273	−0.119, 0.002	−0.217, 0.0007	−0.700, 0.0005	−0.060, 0.489	−0.170, 0.0003
HTGC	−1.44, 0.003	−1.43, 0.004	−1.64, 0.002	−1.46, <0.0001	−3.00, <0.0001	−0.73, 0.283	−1.27, 0.016	−1.81, <0.0001

The models are adjusted for age, race, height, history of hypertension and diabetes, HOMA-IR, TG, low-density lipoprotein, high-density lipoprotein, and alcohol use. Separate models were generated for males and females. β-Coefficients represent change in log adiponectin per change for each percent change (hepatic TG) or kilogram (fat mass).

ethnically and racially diverse, population-based cohort for the first time. Unlike previous studies, the format of the DHS is relatively immune from referral bias, and the large sample size allows for control of confounders in the analysis. The results of this study demonstrated the association between adiponectin and liver fat as both a categorical and continuous variable. This relationship remained significant despite controlling for visceral adipose tissue. The findings from this study suggest that the inverse relationship between adiponectin and hepatic steatosis occurs largely irrespective of gender and race/ethnicity, and the association between adiponectin and steatosis remained the most robust independent relationship of all measured intraabdominal fat depots. Interestingly, however, the relationship between abdominal adiposity and adiponectin was less robust among the Hispanic population.

Previous reports examining the relationship between adiponectin and hepatic steatosis have been relatively small case-control studies (7–10). The limitations of such studies include potential selection bias and the inability to appropriately control for potential confounders due to lack of power or technical issues with data collection. The present data extend the work of previous investigators and, for the first time, demonstrate that the relationship between adiponectin and liver TG content persists even after controlling for intraabdominal adiposity.

Murine models have provided us with some important insights into the potential role of adiponectin in the accumulation of liver fat. The insulin resistance and ectopic lipid deposition (including in the liver) phenotypes of the *ob*/*ob* mouse can be significantly improved by modest (2- to 3-fold) transgenic overproduction of adiponectin in adipose tissue (9). Similar reductions in HTGC were seen during high-fat diet (HFD) feeding on an adiponectin-overexpressing background compared with wild-type mice (14). By analyzing hepatic lipid content longitudinally using computer tomographic methods, adiponectin overexpression in mice was found to be protective against both the acute and the chronic effects of HFD-induced lipotoxicity in the liver (15). In fact, elevated adiponectin levels reduced the HFD-induced hepatomegaly and allowed these mice to gain significantly less hepatic weight per unit increase in whole-body weight. The detailed mechanisms that led to the selective improvements in the liver remain to be defined. However, the ability of these mice to enhance lipid deposition in the sc fat pads as well as the stimulatory effects of adiponectin on local ceramidase activity in liver that leads to improved insulin sensitivity (16) are likely to be contributing factors.

Although adiponectin concentrations were significantly associated with each component of intraabdominal adiposity, including hepatic fat, in Blacks and Whites, we observed less robust univariate correlations in Hispanics. In fact, in multivariate analysis, adiponectin levels were no longer significantly correlated with the degree of hepatic steatosis among Hispanic men. This finding suggests that there may be other potential drivers of hepatic fat in this population. One possibility is the I148M sequence variant in patatin-like phospholipase domain-containing 3 (PNPLA3 or adiponutrin). This mutation is relatively common in Hispanics and is independently associated with the presence of liver fat, possibly leading to some degree of dissociation of this measure from adiposity (17).

There are several limitations of this study. The cross-sectional nature allows us to find associations between variables, but we are unable to draw conclusions regarding causality. Hence, it remains unanswered from this analysis whether adiponectin causes hepatic TG accumulation or is simply a marker of this process. Second, our determination of HTGC is derived from ^{1}H-MRS-based measurements. Although this method has been shown to correlate well with the results from biopsies (13, 18) and is generally regarded as the best noninvasive assessment of HTGC, we do not have tissue-level quantification of liver fat. Furthermore, we are unable to exclude other forms of liver disease (*e.g.* hepatitis C genotype 3) that might also present with steatosis as a prominent feature, although we would expect these numbers to be relatively low in this cohort. Given the practical difficulties in doing glucose clamps on this large cohort, we were dependent on HOMA-IR measurements as a surrogate for insulin sensitivity. This method has limitations in terms of sensitivity and specificity. Finally, we did not subquantify levels of oligomeric forms of adiponectin in this cohort. Much of the biological action of adiponectin may arise from the high-molecular-weight isoforms (19, 20).

In conclusion, these results from a large, multiethnic population-based cohort shows that 1) the previously observed inverse association between adiponectin and hepatic steatosis persists even after controlling for measures of insulin sensitivity and extrahepatic abdominal adiposity; 2) it generally extends across race/ethnicities, with some attenuation in the Hispanic population; and 3) it is valid in a large, nonselected, population-based cohort. Additional studies are needed to determine whether adiponectin may be causally implicated in the pathogenesis of hepatic steatosis in humans.

Acknowledgments

We thank Laura Brulé in the Metabolic Core Facility for adiponectin measurements.

Address all correspondence and requests for reprints to: Aslan T. Turer, M.D., University of Texas Southwestern Medical Center, 5323 Harry Hines Boulevard, Dallas, Texas 75390-8521. E-mail: Aslan.Turer@UTSouthwestern.edu.

Disclosure Summary: The authors have no disclosures to report.

References

1. **Browning JD, Szczepaniak LS, Dobbins R, Nuremberg P, Horton JD, Cohen JC, Grundy SM, Hobbs HH** 2004 Prevalence of hepatic steatosis in an urban population in the United States: impact of ethnicity. Hepatology 40:1387–1395
2. **Bedogni G, Miglioli L, Masutti F, Tiribelli C, Marchesini G, Bellentani S** 2005 Prevalence of and risk factors for nonalcoholic fatty liver disease: the Dionysos nutrition and liver study. Hepatology 42:44–52
3. **Weston SR, Leyden W, Murphy R, Bass NM, Bell BP, Manos MM, Terrault NA** 2005 Racial and ethnic distribution of nonalcoholic fatty liver in persons with newly diagnosed chronic liver disease. Hepatology 41:372–379
4. **Donnelly KL, Smith CI, Schwarzenberg SJ, Jessurun J, Boldt MD, Parks EJ** 2005 Sources of fatty acids stored in liver and secreted via lipoproteins in patients with nonalcoholic fatty liver disease. J Clin Invest 115:1343–1351
5. **Ouchi N, Kihara S, Arita Y, Okamoto Y, Maeda K, Kuriyama H, Hotta K, Nishida M, Takahashi M, Muraguchi M, Ohmoto Y, Nakamura T, Yamashita S, Funahashi T, Matsuzawa Y** 2000 Adiponectin, an adipocyte-derived plasma protein, inhibits endothelial NF-κB signaling through a cAMP-dependent pathway. Circulation 102:1296–1301
6. **Fruebis J, Tsao TS, Javorschi S, Ebbets-Reed D, Erickson MR, Yen FT, Bihain BE, Lodish HF** 2001 Proteolytic cleavage product of 30-kDa adipocyte complement-related protein increases fatty acid oxidation in muscle and causes weight loss in mice. Proc Natl Acad Sci USA 98:2005–2010
7. **Yamauchi T, Kamon J, Waki H, Terauchi Y, Kubota N, Hara K, Mori Y, Ide T, Murakami K, Tsuboyama-Kasaoka N, Ezaki O, Akanuma Y, Gavrilova O, Vinson C, Reitman ML, Kagechika H, Shudo K, Yoda M, Nakano Y, Tobe K, Nagai R, Kimura S, Tomita M, Froguel P, Kadowaki T** 2001 The fat-derived hormone adiponectin reverses insulin resistance associated with both lipoatrophy and obesity. Nat Med 7:941–946
8. **Berg AH, Combs TP, Du X, Brownlee M, Scherer PE** 2001 The adipocyte-secreted protein Acrp30 enhances hepatic insulin action. Nat Med 7:947–953
9. **Kim JY, van de Wall E, Laplante M, Azzara A, Trujillo ME, Hofmann SM, Schraw T, Durand JL, Li H, Li G, Jelicks LA, Mehler MF, Hui DY, Deshaies Y, Shulman GI, Schwartz GJ, Scherer PE** 2007 Obesity-associated improvements in metabolic profile through expansion of adipose tissue. J Clin Invest 117:2621–2637
10. **Polyzos SA, Toulis KA, Goulis DG, Zavos C, Kountouras J** 2011 Serum total adiponectin in nonalcoholic fatty liver disease: a systematic review and meta-analysis. Metabolism 60:313–326
11. **Victor RG, Haley RW, Willett DL, Peshock RM, Vaeth PC, Leonard D, Basit M, Cooper RS, Iannacchione VG, Visscher WA, Staab JM, Hobbs HH; Dallas Heart Study Investigators** 2004 The Dallas Heart Study: a population-based probability sample for the multidisciplinary study of ethnic differences in cardiovascular health. Am J Cardiol 93:1473–1480
12. **Abate N, Garg A, Coleman R, Grundy SM, Peshock RM** 1997 Prediction of total subcutaneous abdominal, intraperitoneal, and retroperitoneal adipose tissue masses in men by a single axial magnetic resonance imaging slice. Am J Clin Nutr 65:403–408
13. **Szczepaniak LS, Babcock EE, Schick F, Dobbins RL, Garg A, Burns DK, McGarry JD, Stein DT** 1999 Measurement of intracellular triglyceride stores by ^{1}H spectroscopy: validation in vivo. Am J Physiol 276:E977–E989
14. **Yamauchi T, Kamon J, Waki H, Imai Y, Shimozawa N, Hioki K, Uchida S, Ito Y, Takakuwa K, Matsui J, Takata M, Eto K, Terauchi Y, Komeda K, Tsunoda M, Murakami K, Ohnishi Y, Naitoh T, Yamamura K, Ueyama Y, Froguel P, Kimura S, Nagai R, Kadowaki T** 2003 Globular adiponectin protected *ob/ob* mice from diabetes and *ApoE*-deficient mice from atherosclerosis. J Biol Chem 278:2461–2468
15. **Asterholm IW, Scherer PE** 2010 Enhanced metabolic flexibility associated with elevated adiponectin levels. Am J Pathol 176:1364–1376
16. **Holland WL, Miller RA, Wang ZV, Sun K, Barth BM, Bui HH, Davis KE, Bikman BT, Halberg N, Rutkowski JM, Wade MR, Tenorio VM, Kuo MS, Brozinick JT, Zhang BB, Birnbaum MJ, Summers SA, Scherer PE** 2011 Receptor-mediated activation of ceramidase activity initiates the pleiotropic actions of adiponectin. Nat Med 17:55–63
17. **Romeo S, Kozlitina J, Xing C, Pertsemlidis A, Cox D, Pennacchio LA, Boerwinkle E, Cohen JC, Hobbs HH** 2008 Genetic variation in PNPLA3 confers susceptibility to nonalcoholic fatty liver disease. Nat Genet 40:1461–1465
18. **Longo R, Pollesello P, Ricci C, Masutti F, Kvam BJ, Bercich L, Crocè LS, Grigolato P, Paoletti S, de Bernard B** 1995 Proton MR spectroscopy in quantitative in vivo determination of fat content in human liver steatosis. J Magn Reson Imaging 5:281–285
19. **Hara K, Horikoshi M, Yamauchi T, Yago H, Miyazaki O, Ebinuma H, Imai Y, Nagai R, Kadowaki T** 2006 Measurement of the high-molecular weight form of adiponectin in plasma is useful for the prediction of insulin resistance and metabolic syndrome. Diabetes Care 29:1357–1362
20. **Zhu N, Pankow JS, Ballantyne CM, Couper D, Hoogeveen RC, Pereira M, Duncan BB, Schmidt MI** 2010 High-molecular-weight adiponectin and the risk of type 2 diabetes in the ARIC study. J Clin Endocrinol Metab 95:5097–5104