Available online at www.sciencedirect.com

SCIENCE DIRECT®

Metabolism Clinical and Experimental 54 (2005) 775–780

Metabolism
Clinical and Experimental

www.elsevier.com/locate/metabol

Inverse correlation between serum adiponectin concentration and hepatic lipid content in Japanese with type 2 diabetes☆

Kengo Maeda, Keiko Ishihara, Kazuaki Miyake, Yasushi Kaji, Hideaki Kawamitsu, Masahiko Fujii, Kazuro Sugimura, Takeshi Ohara*

Division of Diabetes and Digestive and Kidney Diseases, Department of Clinical Molecular Medicine, Kobe University Graduate School of Medicine, Kobe 650-0017, Japan

Department of Radiology, Kobe University Graduate School of Medicine, Kobe 650-0017, Japan

Received 27 July 2004; accepted 7 January 2005

Abstract

Adiponectin is an adipose tissue-specific protein and plays an important role in insulin sensitivity. On the other hand, intramyocellular lipid content and hepatic lipid content (HLC) are related to insulin resistance in humans. In the present study, the possible relations between the serum concentration of adiponectin and intracellular triglyceride content in skeletal muscle and in the liver were investigated in individuals with type 2 diabetes mellitus. Fifty Japanese sedentary subjects (34 men, 16 women) with type 2 diabetes who had neither been treated with insulin nor with thiazolidinediones were enrolled in the study. Insulin sensitivity in vivo was evaluated by measurement of the glucose infusion rate during a hyperinsulinemic-euglycemic clamp and of the homeostasis model of assessment-insulin resistance index. The intracellular triglyceride content in skeletal muscle and the liver was determined by nuclear magnetic resonance. The serum adiponectin concentration was inversely correlated with both HLC ($r = -0.39$, $P < .01$) and the homeostasis model of assessment-insulin resistance index ($r = -0.32$, $P < .05$), but it was not significantly related to either intramyocellular lipid content or glucose infusion rate during the hyperinsulinemic-euglycemic clamp in individuals with type 2 diabetes. These results suggest that adiponectin might play an important role in the regulation of HLC and basal insulin sensitivity in individuals with type 2 diabetes.

1. Introduction

Adiponectin (also known as GBP28, AdipoQ, and Acrp30) [1-4] is an adipose tissue–specific protein that is also abundant in the circulation. The plasma concentration of adiponectin is reduced in individuals with obesity, type 2 diabetes mellitus, or coronary artery disease [5], and is inversely correlated with insulin resistance in humans [6-15]. Adiponectin knockout mice exhibit insulin resistance [16,17], and treatment of diabetic animals with adiponectin markedly ameliorates insulin resistance [18]. These various observations suggest that adiponectin is an important determinant of insulin sensitivity.

Proton nuclear magnetic resonance spectroscopy allows the noninvasive measurement of intracellular triglyceride content in skeletal muscle and the liver [19]. Both intramyocellular lipid content (IMCL) [20-23] and hepatic lipid content (HLC) [24-28] are related to insulin resistance in humans. Whereas muscle-specific overexpression of lipoprotein lipase in mice induces muscle-specific insulin resistance and increases the triglyceride content of muscle, liver-specific overexpression of this enzyme results in liver-specific insulin resistance and increases hepatic triglyceride content [29]. Intracellular lipid content in skeletal muscle and the liver is therefore also thought to play an important role in insulin resistance.

☆ This work was supported in part by a grant for the 21st Century COE Program, "Center of Excellence for Signal Transduction Disease: Diabetes Mellitus as Model," from the Ministry of Education, Culture, Sports, Science, and Technology of Japan and by a grant from the Cooperative Link of Unique Science and Technology for Economy Revitalization (CLUSTER).

* Corresponding author. Division of Diabetes and Digestive and Kidney Diseases, Department of Clinical Molecular Medicine, Kobe University Graduate School of Medicine, Kobe 650-0017, Japan. Tel.: +81 78 382 5861; fax: +81 78 382 2080.

E-mail address: ohara@med.kobe-u.ac.jp (T. Ohara).

0026-0495/$ – see front matter © 2005 Elsevier Inc. All rights reserved.
doi:10.1016/j.metabol.2005.01.020

Table 1
Clinical and laboratory characteristics of the study subjects (n = 50)

Characteristic	Mean ± SD
Age (y)	57 ± 14
BMI (kg m^{-2})	25.5 ± 3.7
Visceral fat area (cm^2)	105.6 ± 47
Fasting plasma glucose (mmol L^{-1})	7.4 ± 1.8
Fasting serum insulin (pmol L^{-1})	46.8 ± 35
Insulin-stimulated glucose disposal (mg kg^{-1} min^{-1})	5.53 ± 1.85
Serum adiponectin (μg mL^{-1})	5.3 ± 3.3

BMI indicates body mass index.

We have now investigated the possible relations between the serum concentration of adiponectin and intracellular triglyceride content in skeletal muscle and in the liver in Japanese subjects with type 2 diabetes mellitus.

2. Subjects and methods

2.1. Subjects

Fifty Japanese sedentary subjects (34 men, 16 women) with type 2 diabetes who had neither been treated with insulin nor with thiazolidinediones were enrolled in the study. The clinical and laboratory characteristics of these individuals are shown in Table 1. The study was performed with written informed consent from all subjects and was approved by the Ethics Committee of Kobe University Graduate School of Medicine.

2.2. Determination of the triglyceride content of skeletal muscle

Single-voxel ^{1}H spectra were acquired from the soleus muscle with a conventional circumferential extremity coil on a 1.5-T magnetic resonance machine (Signa Echo Speed; GE Yokogawa Medical Systems, Hino, Japan). Localizer images were obtained to position the volume of interest. A point resolved spectroscopy pulse sequence (repetition time, 3000 milliseconds; echo time, 50 milliseconds) was used, and 64 averages were accumulated with conventional water signal suppression (acquisition time, 252 seconds). The voxel size was 15 × 15 × 15 mm^3. Data processing (apodization, Fourier transformation, phase correction, baseline correction) was performed with Functool Software (GE Yokogawa Medical Systems). The integral of the methylene signal at 1.4 ppm was calculated with NIH Image software (NIH, Bethesda, Md) to represent IMCL, and the integral of the methylene signal at 1.6 ppm was calculated to represent extramyocellular triglyceride content. The integral of the creatine signal at 3.1 ppm served as an internal standard for quantitation of IMCL [19].

2.3. Determination of liver triglyceride content

We used the fast spoiled gradient recalled acquisition in the steady state sequence to obtain in-phase and out-of-phase images of the liver (flip angle, 75°; TR, 120 milliseconds; TE, 1.8 and 4.2 milliseconds for out-of phase and in-phase images, respectively; matrix, 256 × 160; FOV, 32 × 24; acquisition time, 15 seconds). Hepatic lipid content was determined from the index of the fast spoiled gradient recalled acquisition in the steady state sequence: [(intensities of in-phase) − (intensities of out-of-phase)]/[(intensities of in-phase) + (intensities of out-of-phase)]. We found that this method was as useful as ^{1}H magnetic resonance spectroscopy and less time-consuming [30].

2.4. Determination of intra-abdominal fat areas

A series of T1-weighted transaxial scans for the determination of visceral and subcutaneous fat areas was acquired from a region extending from 4 cm above to 4 cm below the fourth and fifth lumbar interspace (16 slices; slice thickness, 10 mm). Areas of visceral and subcutaneous fat were measured with NIH Image software.

2.5. Hyperinsulinemic-euglycemic clamp

Teflon catheters were inserted into the antecubital vein of one arm for blood collection and into that of the other arm for infusion of glucose and insulin. Regular human insulin was infused intravenously at 1.46 mU kg^{-1} min^{-1} to achieve a serum insulin concentration of 600 pmol L^{-1}, and plasma glucose concentration was maintained at 5.5 mmol L^{-1} by a variable infusion of glucose. The hyperinsulinemic-euglycemic clamp was maintained for at least 2 hours. The rate of glucose infusion (GIR), expressed in milligrams per kilogram per minute, required to maintain euglycemia

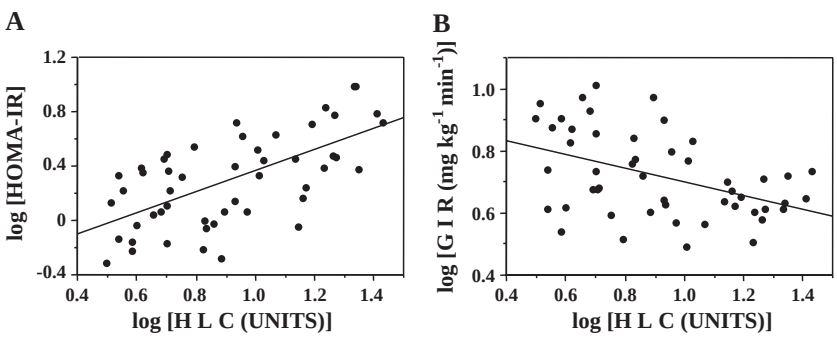

Fig. 1. Relations between insulin sensitivity and hepatic lipid content. A, Relation between log HOMA-IR index and log HLC (U) (r = 0.63, P < .0001, n = 50). B, Relation between log GIR and log HLC (U) (r = −0.44, P < .01, n = 50).

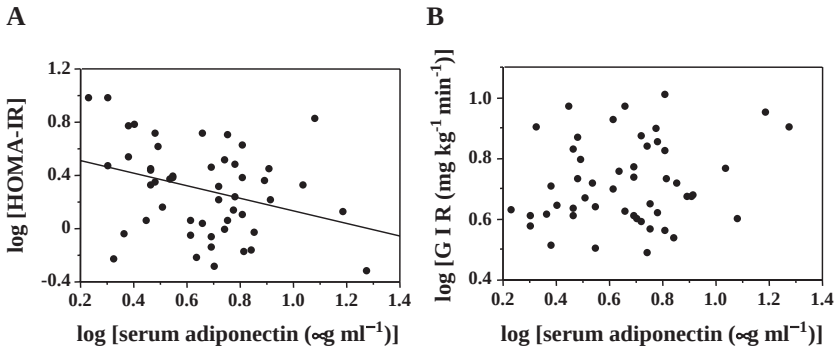

Fig. 2. Relations between serum adiponectin concentration and insulin sensitivity. A, Relation between log HOMA-IR index and log serum adiponectin concentration ($r = -0.32$, $P < .05$, $n = 50$). B, Relation between log GIR and log serum adiponectin concentration ($r = 0.19$, $P > .05$, $n = 50$).

during hyperinsulinemia was used as an estimate of insulin-stimulated total-body glucose uptake [31].

2.6. Assay of glucose, insulin, and adiponectin

Plasma glucose concentration was determined by the glucose oxidase method. Serum insulin concentration was measured with a sandwich enzyme immunoassay system (Tosoh, Tokyo, Japan). Serum adiponectin level was measured using a commercially available sandwich enzyme–linked immunosorbent assay kit (Otsuka Pharmaceuticals Co, Ltd) as previously described [5]. Briefly, 10 μL of serum was mixed with 90 ìl of the sample buffer containing 2.3% sodium dodecyl sulfate and boiled for 5 minutes. Sequentially, the sample was diluted and applied to each well of the plate coated with the monoclonal antibody against adiponectin. The wells were washed and incubated with antirabbit serum against adiponectin. After washing, the binding of the rabbit antibody was determined by horseradish peroxidase method. The homeostasis model of assessment-insulin resistance (HOMA-IR) index was calculated as [fasting plasma glucose concentration (mmol L^{-1}) × fasting serum insulin concentration (mU L^{-1})]/22.5 [32].

2.7. Statistical analysis

Averaged data are presented as means ± SD. Statistical analysis was performed with the Stat-View program (version 5.0-J; SAS Institute, Cary, NC). Serum adiponectin concentrations, the HOMA-IR index, the GIR, HLC, and IMCL were expressed as log values to achieve a more normal distribution. Relations between variables were assessed by simple correlation and multiple linear regression analyses. A P value of ≤.05 was considered statistically significant.

3. Results

The HOMA-IR index was significantly correlated with HLC (log [HOMA-IR] vs log [HLC], $r = 0.64$, $P < .0001$) (Fig. 1A) but not with IMCL. The GIR during the hyperinsulinemic-euglycemic clamp was inversely correlated with both HLC (log [GIR] vs log [HLC], $r = -0.44$, $P < .01$) (Fig. 1B) and IMCL (log [GIR] vs log [IMCL], $r = -0.35$, $P < .05$). The serum concentration of adiponectin was slightly higher in women (5.9 ± 2.8 μg mL^{-1}) than in men (5.0 ± 3.5 μg mL^{-1}), but this difference was not statistically significant. The serum adiponectin concentration was significantly correlated with age ($r = 0.33$, $P < .05$) but not with either BMI ($r = -0.11$, $P > .05$), visceral fat area ($r = 0.02$, $P > .05$), or subcutaneous fat area ($r = -0.16$, $P > .05$). It was inversely correlated with the HOMA-IR index (log [adiponectin] vs log [HOMA-IR], $r = -0.32$, $P < .05$) (Fig. 2A), but it was not significantly related to GIR (Fig. 2B). Finally, the serum concentration of adiponectin was inversely correlated with HLC (log [adiponectin] vs log [HLC], $r = -0.39$, $P < .01$)

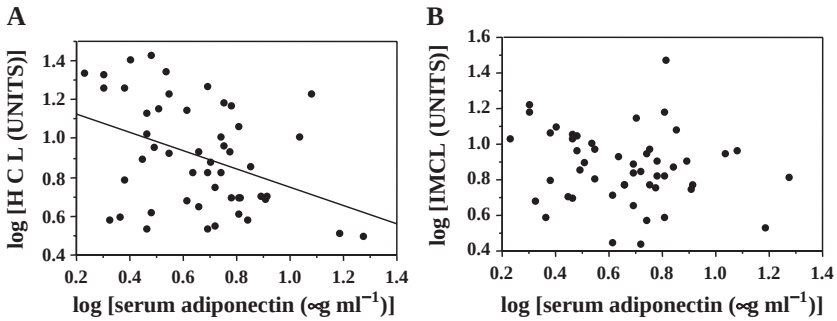

Fig. 3. Relations between serum adiponectin concentration and intracellular lipid content in the liver and skeletal muscle. A, Relation between log HLC (U) and log serum adiponectin concentration ($r = -0.39$, $P < .01$, $n = 50$). B, Relation between log IMCL (U) and log serum adiponectin concentration ($r = -0.18$, $P > .05$, $n = 50$).

(Fig. 3A), but it was not significantly related to IMCL (Fig. 3B). Multiple linear regression analysis revealed that the associations between the serum adiponectin concentration and both the HOMA-IR index (log [HOMA-IR], $r = -0.28$, $P < .01$) and HLC (log [HLC], $r = -0.37$, $P < .01$) remained significant after adjustment for age, sex, and BMI.

4. Discussion

We evaluated insulin sensitivity in vivo by measuring the GIR during a hyperinsulinemic-euglycemic clamp as well as the HOMA-IR index. It is thought that the HOMA and euglycemic clamp provide estimates of basal and stimulated insulin resistance, respectively, and that basal insulin resistance may differ mechanistically from stimulated insulin resistance [33]. When the serum insulin concentration is maintained at a high level (600 pmol L^{-1}) during a hyperinsulinemic-euglycemic clamp, the GIR required to maintain euglycemia (5.5 mmol L^{-1}) represents whole-body insulin sensitivity, which is mostly determined by the ability of skeletal muscle to take up glucose. In contrast, glucose homeostasis in the postabsorptive state is maintained predominantly by hepatic glucose production. Homeostasis model of assessment has previously been shown to correlate well with hepatic insulin sensitivity measured with [^{3}H] glucose under postabsorptive conditions, while HOMA also correlates with whole-body insulin sensitivity measured by the hyperinsulinemic-euglycemic clamp [34]. Because plasma insulin levels may widely vary depending on the capacity for pancreatic insulin secretion, plasma insulin will be lower and this will not accurately reflect insulin resistance when a patient's pancreas is failing. There are some limitations to evaluating insulin sensitivity in vivo especially in subjects with type 2 diabetes by the HOMA-IR index and the GIR during hyperinsulinemic-euglycemic clamp without tracer.

Previous studies have demonstrated an inverse correlation between IMCL and insulin sensitivity, as evaluated with a hyperinsulinemic-euglycemic clamp, in nondiabetic subjects (20-23), although the relation between these parameters appears both to differ among populations of different ethnicities, such as Europeans and South Asians [35], and to be dependent on other physiological conditions [36-38]. Hepatic lipid content has also been found to be correlated inversely with insulin sensitivity, as evaluated with a hyperinsulinemic-euglycemic clamp [24,25], as well as to be inversely related to the ability of intravenously administered insulin to inhibit glucose production in individuals with type 2 diabetes or nonalcoholic fatty liver disease [26-28].

We have now shown that the HOMA-IR index was highly correlated with HLC but was not related to IMCL, whereas the GIR was inversely correlated with both HLC and IMCL, in sedentary subjects with type 2 diabetes. Our data suggest that basal insulin resistance may be related mostly to hepatic lipid content, whereas stimulated insulin resistance may be related to both HLC and IMCL.

Adiponectin enhances insulin action in the liver and reduces hepatic glucose production in mice [39,40]. This hormone is thought to modulate gluconeogenesis and lipogenesis in the liver by down-regulating the hepatic expression of phosphoenolpyruvate carboxykinase and sterol regulatory element–binding protein 1c [41], and it alleviates alcoholic and nonalcoholic fatty liver by increasing hepatic carnitine palmitoyltransferase-1 activity and fatty acid oxidation [42]. Furthermore, treatment of diabetic mice with adiponectin markedly increases insulin sensitivity by reducing the triglyceride content of muscle and liver [18].

Our present data show that the serum concentration of adiponectin was inversely correlated with the HOMA-IR index in individuals with type 2 diabetes, despite the fact that the serum concentration of this hormone was not correlated with either BMI or intra-abdominal fat area. We did not detect a significant relation between serum adiponectin concentration and GIR, although the plasma adiponectin concentration was previously shown to be negatively associated with the rate of insulin-stimulated glucose disposal in nondiabetic subjects [13-15].

The serum adiponectin concentration was also inversely correlated with HLC, but it was not related to IMCL, in our type 2 diabetic subjects. The serum concentration of adiponectin was previously shown to be inversely correlated with IMCL in nondiabetic subjects [43,44]. These discrepancies might be due to differences between diabetic and nondiabetic subjects or to differences among races.

The plasma adiponectin concentrations were negatively associated with basal and insulin-suppressed endogenous glucose production in nondiabetic subjects [45,46]. The negative correlation between serum adiponectin levels and hepatic fat content was shown in subjects with type 2 diabetes and highly active antiretroviral therapy–associated lipodystrophy [47,48]. Only full-length adiponectin activates adenosine 5′ -monophosphate–activated protein kinase in the liver, whereas globular adiponectin activates adenosine 5′ -monophosphate–activated protein kinase more potently than does full-length adiponectin in skeletal muscle [49,50]. These observations suggest that adiponectin may regulate intracellular triglyceride content in the liver as well as hepatic insulin sensitivity.

As far as we are aware, our present investigation is the first study to examine the relations between the serum adiponectin concentration and intracellular lipid content in both the liver and skeletal muscle at the same time. Our observations suggest that adiponectin might regulate intracellular triglyceride content in the liver rather than in skeletal muscle and might contribute to basal insulin sensitivity rather than to stimulated insulin sensitivity in individuals with type 2 diabetes.

In summary, the HOMA-IR index, which represents basal insulin resistance, was highly correlated with HLC, whereas the GIR, which represents stimulated insulin sensitivity, was inversely correlated with both HLC and

IMCL, in Japanese sedentary individuals with type 2 diabetes. The serum adiponectin concentration was negatively correlated with the HOMA-IR index and HLC, but was not related to the GIR or IMCL, in these individuals.

Acknowledgments

We thank Masato Kasuga for supervision of the present work and valuable discussions.

References

[1] Scherer PE, Williams S, Fogliano M, et al. A novel serum protein similar to C1q, produced exclusively in adipocytes. J Biol Chem 1995;270:26746-9.

[2] Maeda K, Okubo K, Shimomura I, et al. cDNA cloning and expression of a novel adipose specific collagen-like factor, apM1 (adipose most abundant gene transcript 1). Biochem Biophys Res Commun 1996; 221:286-9.

[3] Hu E, Liang P, Spiegelman BM. AdipoQ is a novel adipose-specific gene dysregulated in obesity. J Biol Chem 1996;271:10697-703.

[4] Nakano Y, Tobe T, Choi-Miura NH, et al. Isolation and characterization of GBP28, a novel gelatin-binding protein purified from human plasma. J Biochem (Tokyo) 1996;120:803-12.

[5] Hotta K, Funahashi T, Arita Y, et al. Plasma concentrations of a novel, adipose-specific protein, adiponectin, in type 2 diabetic patients. Arterioscler Thromb Vasc Biol 2000;20:1595-9.

[6] Yamamoto Y, Hirose H, Saito I, et al. Correlation of the adipocyte-derived protein adiponectin with insulin resistance index and serum high-density lipoprotein-cholesterol, independent of body mass index, in the Japanese population. Clin Sci 2002;103:137-42.

[7] Kern PA, Di Gregorio GB, Lu T, et al. Adiponectin expression from adipose tissue: relation to obesity, insulin resistance, and tumor necrosis factor-alpha expression. Diabetes 2003;52:1779-85.

[8] Pellme F, Smith U, Funahashi T, et al. Circulating adiponectin levels are reduced in nonobese but insulin-resistant first-degree relatives of type 2 diabetic patients. Diabetes 2003;52:1182-6.

[9] Cnop M, Havel PJ, Utzschneider KM, et al. Relationship of adiponectin to body fat distribution, insulin sensitivity and plasma lipoproteins: evidence for independent roles of age and sex. Diabetologia 2003;46:459-69.

[10] Matsubara M, Katayose S, Maruoka S. Decreased plasma adiponectin concentrations in nondiabetic women with elevated homeostasis model assessment ratio. Eur J Endocrinol 2003;148:343-50.

[11] Weyer C, Funahashi T, Tanaka S, et al. Hypoadiponectinemia in obesity and type 2 diabetes: close association with insulin resistance and hyperinsulinemia. J Clin Endocrinol Metab 2001;86:1930-5.

[12] Yu JG, Javorschi S, Hevener AL, et al. The effect of thiazolidinediones on plasma adiponectin levels in normal, obese, and type 2 diabetic subjects. Diabetes 2002;51:2968-74.

[13] Stefan N, Vozarova B, Funahashi T, et al. Plasma adiponectin concentration is associated with skeletal muscle insulin receptor tyrosine phosphorylation, and low plasma concentration precedes a decrease in whole-body insulin sensitivity in humans. Diabetes 2002; 51:1884-8.

[14] Tschritter O, Fritsche A, Thamer C, et al. Plasma adiponectin concentrations predict insulin sensitivity of both glucose and lipid metabolism. Diabetes 2003;52:239-43.

[15] Furuhashi M, Ura N, Higashiura K, et al. Blockade of the renin-angiotensin system increases adiponectin concentrations in patients with essential hypertension. Hypertension 2003;42:76-81.

[16] Kubota N, Terauchi Y, Yamauchi T, et al. Disruption of adiponectin causes insulin resistance and neointimal formation. J Biol Chem 2002; 277:25863-6.

[17] Maeda N, Shimomura I, Kishida K, et al. Diet-induced insulin resistance in mice lacking adiponectin/ACRP30. Nat Med 2002;8: 731-7.

[18] Yamanouchi T, Kamon J, Waki H, et al. The fat-derived hormone adiponectin reverses insulin resistance associated with both lipoatrophy and obesity. Nat Med 2001;7:941-6.

[19] Szcxepaniak LS, Babcock EE, Schick F, et al. Measurement of intracellular triglyceride stores by ^{1}H spectroscopy: validation in vivo. Am J Physiol 1999;276:E977-89.

[20] Perseghin G, Scifo P, Cobelli FD, et al. Intramyocellular triglyceride content is a determinant of in vivo insulin resistance in humans: a ^{1}H-^{13}C nuclear magnetic resonance spectroscopy assessment in offspring of type 2 diabetic parents. Diabetes 1999;48:1600-6.

[21] Krssak M, Petersen KF, Dresner A, et al. Intramyocellular lipid concentrations are correlated with insulin sensitivity in humans: a ^{1}H NMR spectroscopy study. Diabetologia 1999;42:113-6.

[22] Jacob S, Machann J, Rett K, et al. Association of increased intramyocellular lipid content with insulin resistance in lean nondiabetic offspring of type 2 diabetic subjects. Diabetes 1999;48:1113-9.

[23] Virkamaki A, Korsheninnikova E, Seppala-Lindroos A, et al. Intramyocellular lipid is associated with resistance to in vivo insulin actions on glucose uptake, antilipolysis, and early insulin signaling pathways in human skeletal muscle. Diabetes 2001;50:2337-43.

[24] Banerji MA, Buckley MC, Chaiken RL, et al. Liver fat, serum trglycerides and visceral adipose tissue in insulin-sensitive and insulin-resistant black men with NIDDM. Int J Obes Relat Metab Disord 1995;19:839-40.

[25] Goto T, Onuma T, Takabe K, et al. The influence of fatty liver on insulin clearance and insulin resistance in non-diabetic Japanese subjects. Int J Obes Relat Metab Disord 1995;19:841-5.

[26] Ryysy L, Hakkinen AM, Goto T, et al. Hepatic fat content and insulin action on free fatty acids and glucose metabolism rather than insulin absorption are associated with insulin requirements during insulin therapy in type 2 diabetic patients. Diabetes 2000;49:749-58.

[27] Seppala-Lindroos A, Vehkavaara S, Hakkinen AM, et al. Fat accumulation in the liver is associated with defects in insulin suppression of glucose production and serum free fatty acids independent of obesity in normal men. J Clin Endocrinol Metab 2002;87:3023-8.

[28] Marchesini G, Brizi M, Bianchi G, et al. Nonalcoholic fatty liver disease. Diabetes 2001;50:1844-50.

[29] Kim JK, Fillmore JJ, Chen Y, et al. Tissue-specific overexpression of lipoprotein lipase causes tissue-specific insulin resistance. Proc Natl Acad Sci U S A 2001;98:7522-7.

[30] Kawamitsu H, Kaji Y, Ohara T, et al. Feasibility of quantitative intrahepatic lipid imaging applied to the magnetic resonance dual gradient echo sequence. Magn Reson Med Sci 2003;2:47-51.

[31] DeFronzo RA, Tobin JD, Andres R. Glucose clamp technique: a method for quantifying insulin secretion and resistance. Am J Physiol 1979;237:E214-23.

[32] Matthews DR, Hosker JP, Rudenski AS, et al. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 1985;28:412-9.

[33] Wallace TM, Matthews DR. The assessment of insulin resistance in man. Diabet Med 2002;19:527-34.

[34] Matsuda M, DeFronzo RA. Insulin sensitivity indices obtained from oral glucose tolerance testing: comparison with the euglycemic insulin clamp. Diabetes Care 1999;22:1462-70.

[35] Forouhi NG, Jenkinson G, Thomas EL, et al. Relation of triglyceride stores in skeletal muscle to central obesity and insulin sensitivity in European and South Asian men. Diabetologia 1999;42:932-5.

[36] Goodpaster BH, He J, Watkins S, Kelley DE. Skeletal muscle lipid content and insulin resistance: evidence for a paradox in endurance-trained athletes. J Clin Endocrinol Metab 2001;86:5755-61.

[37] Thamer C, Machann J, Bachmann O, et al. Intramyocellular lipids: anthropometric determinants and relationships with maximal aerobic

capacity and insulin sensitivity. J Clin Endocrinol Metab 2003;88: 1785-91.
[38] Anderwald C, Bernroider E, Krssak M, et al. Effects of insulin treatment in type 2 diabetic patients on intracellular lipid content in liver and skeletal muscle. Diabetes 2002;51:3025-32.
[39] Berg AH, Combs TP, Du X, Brownlee M, Scherer PE. The adipocyte-secreted protein Acrp 30 enhances hepatic insulin action. Nat Med 2001;7:947-53.
[40] Combs TP, Berg AH, Obici S, et al. Endogenous glucose production is inhibited by the adipose-derived protein Acrp30. J Clin Invest 2001; 108:1875-81.
[41] Shklyaev S, Aslanidi G, Tennant M, et al. Sustained peripheral expression of transgene adiponectin offsets the development of diet-induced obesity in rats. Proc Natl Acad Sci U S A 2003;100: 14217-22.
[42] Xu A, Wang Y, Keshaw H, et al. The fat-derived hormone adiponectin alleviates alcoholic and nonalcoholic fatty liver disease in mice. J Clin Invest 2003;112:91-100.
[43] Thamer C, Machann J, Tschritter O, et al. Relationship between serum adiponectin concentration and intramyocellular lipid stores in humans. Horm Metab Res 2002;34:646-9.
[44] Weiss R, Dufour S, Groszmann A, et al. Low adiponectin levels in adolescent obesity: a marker of increased intramyocellular lipid accumulation. J Clin Endocrinol Metab 2003;88:2014-8.
[45] Stefan N, Stumvoll M, Vozarova B, Weyer C, Funahashi T, Matsuzawa Y, et al. Plasma adiponectin and endogenous glucose production in human. Diabetes Care 2003;26:3315-9.
[46] Bacha F, Saad R, Gungor N, et al. Adiponectin in youth. Diabetes Care 2004;27:547-52.
[47] Sutinen J, Korsheninnikova E, Funahashi T, et al. Circulating concentration of adiponectin and its expression in subcutaneous adipose tissue in patients with highly active antiretroviral therapy-associated lipodystrophy. J Clin Endocrinol Metab 2003;88:1907-10.
[48] Bajaj M, Suraamornkul S, Piper P, et al. Decreased plasma adiponectin concentrations are closely related to hepatic fat content and hepatic insulin resistance in pioglitazone-treated type 2 diabetic patients. J Clin Endocrinol Metab 2004;89:200-6.
[49] Yamauchi T, Kamon Y, Minokoshi Y, et al. Adiponectin stimulates glucose utilization and fatty-acid oxidation by activating AMP-activated protein kinase. Nat Med 2002;8:1288-95.
[50] Yamauchi T, Kamon J, Ito Y, et al. Cloning of adiponectin receptors that mediate antidiabetic metabolic effects. Nature 2003;423:762-9.