[4]Department of Laboratory Medicine, Mie University School of Medicine, Mie, Japan; and the [5]Department of Health and Physical Education, Mie University School of Education, Mie, Japan.

Address correspondence to Y. Sumida, MD, Department of Internal Medicine, Mie University School of Medicine, 2-174 Edobashi, Tsu, Mie, 514-8507, Japan. E-mail: sumidaya@clin.medic.mie-u.ac.jp.

DOI: 10.2337/dc06-1239

References

1. Kadowaki T, Yamauchi T: Adiponectin and adiponectin receptors. *Endocr Rev* 26: 439–451, 2005
2. Matsuzawa Y: The metabolic syndrome and adipocytokines. *FEBS Lett* 580:2917–2921, 2006
3. Hara K, Horikoshi M, Yamauchi T, Yago H, Miyazaki O, Ebinuma H, Imai Y, Nagai R, Kadowaki T: 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, 2006
4. Ruderman N, Chisholm D, Pi-Sunyer X, Schneider S: The metabolically obese, normal-weight individual revisited. *Diabetes* 47:699–713, 1998
5. Karelis AD, St-Pierre DH, Conus F, Rabasa-Lhoret R, Poehlman ET: Metabolic and body composition factors in subgroups of obesity: what do we know? *J Clin Endocrinol Metab* 89:2569–2575, 2004
6. Katsuki A, Sumida Y, Urakawa H, Gabazza EC, Murashima S, Matsumoto K, Nakatani K, Yano Y, Adachi Y: Plasma levels of adiponectin are associated with insulin resistance and serum levels of triglyceride in Japanese metabolically obese, normal-weight men with normal glucose tolerance (Letter). *Diabetes Care* 26:2964–2965, 2003
7. Ebinuma H, Miyazaki O, Yago H, Hara K, Yamauchi T, Kadowaki T: A novel ELISA system for selective measurement of human adiponectin multimers by using proteases. *Clin Chim Acta.* In press
8. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults: Executive summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA* 285: 2486–2497, 2001
9. Katsuki A, Sumida Y, Urakawa H, Gabazza EC, Murashima S, Nakatani K, Yano Y, Adachi Y: Increased oxidative stress is associated with serum levels of triglyceride, insulin resistance, and hyperinsulinemia in Japanese metabolically obese, normal-weight men. *Diabetes Care* 27:631–632, 2004

A Patient With Extreme Insulin Resistance Syndrome Treated With Pioglitazone

Genetic types of extreme insulin resistance include type A insulin resistance syndrome, leprechaunism, congenital generalized lipodystrophy, and Rabson-Mendelhall syndrome (1). Acanthosis nigricans and ovarian masculinization are frequently associated with these syndromes. Genetic defects in insulin action at the receptor or postreceptor levels are responsible for insulin resistance. Since thiazolidinediones enhance insulin sensitivity in patients with insulin resistance, we administered pioglitazone to an insulin-resistant patient with a mutation of the insulin receptor.

A 15-year-old Japanese female was referred to the hospital for an evaluation of hirsutism. Acanthosis nigricans was present in the axillary area and on the neck. She had been amenorrheic since menarche at the age of 12 years. She had two elder sisters, one of whom had the same phenotype. The other sister and the mother of this individual appeared to be unaffected. The father died from laryngiocarcinoma at the age of 45 years after being on hemodialysis due to diabetic renal failure. The patient was normoglycemic (glucose 69 mg/dl) and hyperinsulinemic (immunoreactive insulin [IRI] 148 μU/ml) under fasting conditions. The homeostasis model assessment of insulin resistance was 25.21, and the serum testosterone level was elevated (1.23 ng/ml). A 75-g oral glucose tolerance test generated the following values: glucose 59, 161, 195, and 184 mg/dl and IRI 109, 300, 450, and 695 μU/ml at 0, 30, 60, and 120 min, respectively. Thus, insulin resistance was marked, and hyperandrogenemia was evident. We determined partial DNA sequences of the insulin receptor gene of this patient and found heterogeneous triplet basic deletion from exon 17 of the human insulin receptor gene that resulted in a leucine deletion at amino acid 1,026.

We administered 15 mg/day of pioglitazone. Although fasting glucose levels were not changed, fasting IRI decreased from 148 to 104 μU/ml and HbA_{1c} (A1C) decreased from 6.0 to 4.5% after 5 months. We continued pioglitazone (15 mg/day), and after another 5 months, fasting IRI decreased to 73 μU/ml and A1C to 4.4%. The serum testosterone level decreased from 1.23 to 0.97 ng/ml after 5 months and normalized to 0.68 ng/ml after 10 months. Menstruation recovered after pioglitazone for 2 months. Before treatment, plasma leptin and adiponectin levels were elevated to 15.9 ng/ml and 19.8 μg/ml, respectively. Serum adiponectin increased to 30.5 μg/ml after pioglitazone for 5 months, while the leptin level remained similar.

A number of studies suggest an important link between adiponectin and insulin resistance (2). Although its physiological and pathophysiological role has not been fully elucidated, its low levels in insulin-resistant states suggest that therapeutic modulation of adiponectin may provide a novel treatment modality for insulin resistance (2). Interestingly, the level of adiponectin in this case was not low, but pioglitazone further increased the serum adiponectin level. Thus, pioglitazone might have been beneficial to this patient via both adiponectin-dependent and -independent pathways (3).

The mutation in this patient was situated in the ATP binding site of the insulin receptor β subunit (4). This might disturb the intrinsic tyrosine kinase activity that is essential for signal transduction. However, the means by which the heterogeneous mutation caused insulin resistance remains to be elucidated. Pioglitazone attenuated insulin resistance and ameliorated masculinization. Thus, thiazolidinediones should be considered for treating patients with extreme insulin resistance syndrome. Coadministration of pioglitazone with IGF-1 (5) might be a more optimal treatment strategy for patients with such extreme syndromes.

YOSHIYUKI HATTORI, MD, PHD[1]
HIROKO SATOH, PHD[1]
TAKASHI NAMATAME, PHD[2]
SACHIKO HATTORI, MD, PHD[1]
KIKUO KASAI, MD, PHD[1]

From the [1]Department of Endocrinology and Metabolism, Dokkyo University School of Medicine, Mibu, Japan; and the [2]Institute for Medical Science, Dokkyo University School of Medicine, Mibu, Japan.

Address correspondence to Dr. Yoshiyuki Hattori, MD, PhD, Department of Endocrinology and Metabolism, Dokkyo University School of Medicine, Mibu, Tochigi 321-0293, Japan. E-mail: yhattori@dokkyomed.ac.jp.

DOI: 10.2337/dc05-1249

References

1. Goldfine AB, Moses AC: Syndrome of extreme insulin resistance. In *Joslin's Diabetes Mellitus*. 14th ed. Kahn CR, Weir GC, King GL, Jacobson AM, Moses AC, Smith RJ, Eds. Philadelphia, Lippincott Williams & Wilkins, 2005, p. 493–504
2. Pittas AG, Joseph NA, Greenberg AS: Adipocytokines and insulin resistance. *J Clin Endocrinol Metab* 89:447–452, 2004
3. Kubota N, Terauchi Y, Kubota T, Kumagai H, Itoh S, Satoh H, Yano W, Ogata H, Tokuyama K, Takamoto I, Mineyama T, Ishikawa M, Moroi M, Sugi K, Yamauchi T, Ueki K, Tobe K, Noda T, Nagai R, Kadowaki T: Pioglitazone ameliorates insulin resistance and diabetes by both adiponectin-dependent and -independent pathways. *J Biol Chem* 281:8748–8755, 2006
4. Ullrich A, Bell JR, Chen EY, Herrera R, Petruzzelli LM, Dull TJ, Gray A, Coussens L, Liao YC, Tsubokawa M, Mason A, Seeburg PH, Grunfeld C, Rosen OM, Ramachandran J: Human insulin receptor and its relationship to the tyrosine kinase family of oncogenes. *Nature* 313:756–761, 1985
5. Kuzuya H, Matsuura N, Sakamoto M, Makino H, Sakamoto Y, Kadowaki T, Suzuki Y, Kobayashi M, Akazawa Y, Nomura M, Yoshimasa Y, Kasuga M, Goji K, Nagataki S, Oyasu H, Imura: Trial of insulin-like growth factor I therapy for patients with extreme insulin resistance syndromes. *Diabetes* 42:696–705, 1993

A Continuous Metabolic Syndrome Risk Score

Utility for epidemiological analyses

This study was designed to validate a continuous metabolic syndrome risk score (cMSy) using the International Diabetes Federation risk factors (1). Increasing evidence supports using a cMSy instead of a binary definition for epidemiological analyses: *1*) dichotomizing continuous outcome variables reduces statistical power (2); *2*) cardiovascular risk is a progressive function of several metabolic syndrome (MSy) risk factors, eliminating the need to dichotomize these factors (3); and *3*) cardiovascular and diabetes risk increase progressively with increasing numbers of MSy risk factors, eliminating the need to dichotomize MSy (3–4).

The National Institute of Statistics randomly selected a community sample of 18- to 75-year-old Flemish adults. In total, 571 men (aged 46.7 ± 11.2 years) and 449 women (aged 45.8 ± 10.8 years) without cardiovascular disease and diabetes, tested between October 2002 and April 2004, were included.

Calculation of cMSy involved two steps. First, principal component (PC) analysis (varimax rotation) was applied to the normalized risk factors to derive PCs representing large fractions of MSy variance, revealing two PCs (eigenvalue ≥1.0). In men, PC1 and PC2 explained 33 and 28% of variance, respectively (loadings PC1 [PC2]: waist circumference 0.51 [0.55], triglycerides 0.82 [0.16], HDL cholesterol −0.85 [0.09], blood pressure 0.12 [0.72], and glucose −0.08 [0.73]). In women, PC1 and PC2 explained 33 and 27% of variance, respectively (loadings PC1 [PC2]: waist circumference 0.61 [0.54], triglycerides 0.42 [0.49], HDL cholesterol 0.12 [−0.90], blood pressure 0.83 [0.01], and glucose 0.62 [0.04]). Second, cMSy was computed by summing both individual PC scores, each weighted for the relative contribution of PC1 and PC2 in the explained variance. Resulting cMSy was 0 ± 1.42 in men and 0 ± 1.41 in women.

cMSy was higher ($P < 0.001$) in subjects with MSy as defined by the International Diabetes Federation (1) (men [12.8%]: 2.03 ± 1.00, women [8.5%]: 2.63 ± 1.28) versus subjects without (men: −0.30 ± 1.21, women: −0.24 ± 1.16). Moreover, cMSy increased progressively (Tukey's honestly significant difference comparison, $P < 0.001$) with increasing numbers of risk factors in men (0 [30.1%]: −1.21 ± 0.96; 1 [33.8%]: −0.26 ± 0.87; 2 [21.2%]: 0.67 ± 0.84; 3 [11.2%]: 1.76 ± 0.73; and ≥4 [3.7%]: 3.04 ± 0.94) and women (0 [47.7%]: −0.96 ± 0.79; 1 [28.3%]: 0.16 ± 0.82; 2 [16.3%]: 1.21 ± 0.82; 3 [5.3%]: 2.17 ± 0.81; and ≥4 [2.4%]: 4.09 ± 0.99).

cMSy is a more appropriate (2–4) and valid alternative for epidemiological analyses, although the binary definition (1) remains useful for clinical practice.

KATRIEN WIJNDAELE, MA[1]
GASTON BEUNEN, PHD[2]
NATHALIE DUVIGNEAUD, MA[3]
LYNN MATTON, MA[2]
WILLIAM DUQUET, PHD[3]
MARTINE THOMIS, PHD[2]
JOHAN LEFEVRE, PHD[2]
RENAAT M. PHILIPPAERTS, PHD[1]

From the [1]Department of Movement and Sports Sciences, Ghent University, Ghent, Belgium; the [2]Department of Biomedical Kinesiology, Faculty of Kinesiology and Rehabilitation Sciences, Katholieke Universiteit Leuven, Leuven, Belgium; and the [3]Faculty of Physical Education and Physical Therapy, Vrije Universiteit Brussel, Brussels, Belgium.

Address correspondence to Renaat Philippaerts, PhD, Department of Movement and Sports Sciences, Ghent University, Watersportlaan 2, 9000 Ghent, Belgium. E-mail: renaat.philippaerts@ugent.be

DOI: 10.2337/dc06-1341

Acknowledgments—The Policy Research Centre Sport, Physical Activity and Health is supported by the Flemish government.

References

1. The IDF consensus worldwide definition of the metabolic syndrome [article online], 2005. Available from http://www.idf.org/webdata/docs/Metabolic_syndrome_definition.pdf. Accessed 5 May 2005
2. Ragland DR: Dichotomizing continuous outcome variables: dependence of the magnitude of association and statistical power on the cutpoint. *Epidemiology* 3:434–440, 1992
3. Kahn R, Buse J, Ferrannini E, Stern M: The metabolic syndrome: time for a critical appraisal: joint statement from the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care* 28:2289–2304, 2005
4. Klein BEK, Klein R, Lee KE: Components of the metabolic syndrome and risk of cardiovascular disease and diabetes in Beaver Dam. *Diabetes Care* 25:1790–1794, 2002

Reversibility of Antipsychotic Treatment–Related Diabetes in Patients With Schizophrenia

A case series of switching to aripiprazole

At present, antipsychotic drugs are not specifically referred to in the list of substances that can induce diabetes in the most recent American Diabetes Association guidelines (1), but there is a growing body of evidence that antipsychotic drugs might have diabetogenic properties (2,3). At present, there are no clear guidelines on what the best therapeutic strategies are when diabetes is detected during treatment with antipsy-