□ CASE REPORT □

Low Birth Weight and Insulin Resistance Associated with Lean Body Adiposity in an Adolescent Onset Diabetic Patient

Naoya Igaki, Maki Tanaka and Takeo Goto

Abstract

We describe a patient characterized by reduced fetal growth, no history of rapid “catch-up” growth in pre-pubertal childhood, and adolescent onset diabetes. High doses of insulin were required for glycemic control. Pioglitazone treatment was followed by a deterioration of glycemic control and hepatic steatosis, while metformin treatment was followed by a partial response. Leptin and adiponectin levels were reduced, but a significant increase in leptin and adiponectin levels occurred concomitantly with an increase in weight and adiposity. This case suggests that some fetal genetic factors determining insulin sensitivity might be linked to a reduction in fetal growth as well as the later development of diabetes.

Key words: thrifty phenotype, leptin, adiponectin, lipodystrophy, insulin sensitizer

(DOI: 10.2169/internalmedicine.45.1468)

Introduction

Intrauterine environment and early postnatal life are now generally accepted as important determinants of the risk of disease in adulthood (1-3). Low birth weight, a marker of intrauterine adversity, has consistently been associated with a variety of adult-onset diseases, including type 2 diabetes mellitus, essential hypertension, dyslipidemia, coronary artery disease, and cerebrovascular accidents. The “thrifty phenotype” model posits that the fetus becomes growth retarded in response to adverse environmental conditions in utero, and the associated adaptations induce a phenotype better suited to a deprived postnatal food/energy environment (4). However, recent work (5) stresses that both genetic and environmental factors must be involved, and insulin resistance and compensatory hyperinsulinemia may be the prime pathogenic mechanisms underlying these diseases. On the other hand, the lipodystrophies are rare disorders characterized by selective but variable loss of adipose tissue (6). Metabolic complications, such as insulin resistance, diabetes mellitus, hypertriglyceridemia, and fatty liver, increase in severity with the extent of fat loss as well as low infant birth

weight. However, the prevalence of intrauterine and postnatal growth retardation in congenital lipodystrophies was not clear. Here, we report a patient whose birth weight was low for her gestational age with insulin-resistant type 2 diabetes mediated in part through lean body adiposity.

Case Report

In June 2003, a 23-year-old woman with birth weight of 1800 g at 36 weeks’ gestation was referred to our hospital due to hyperglycemia. On physical examination, her body height was 142.6 cm, body weight 31 kg, body mass index (BMI) 15.2 kg/m², waist circumference 45 cm, and blood pressure 110/64 mmHg. Lean body adiposity was detected (Fig. 1A), but the lower extremities did not show signs of muscular hypertrophy exhibiting prominent superficial veins and muscle. Her medical history was notable for a delayed menarche at the age of 20 and genital herpes simplex at the age of 21, when she was newly diagnosed with diabetes, but she did not recall any acute infectious illnesses. There was no obvious mental retardation or abnormal eating behavior. She received intensive insulin therapy at daily maximal doses of 78 units during six months at the age of 21, but

Department of Internal Medicine, Takasago Municipal Hospital, Takasago

Received for publication June 23, 2005; Accepted for publication October 23, 2005

Reprint requests should be addressed to Naoya Igaki, Department of Internal Medicine, Takasago Municipal Hospital, 33-1 Kamimachi, Arai-cho, Takasago 676-8585

Figure 1. Pre- and post-treatment computed tomography (CT) scans. Decreased liver-to-spleen CT attenuation values (L/S ratio; 1.02) with hepatomegaly, showing slight hepatic steatosis, and the visceral and subcutaneous fat volume was reduced on pre-treatment CT in June 2003 (Fig. 1A).

High doses of insulin in combination with pioglitazone decreased the L/S ratio to 0.98, suggesting deteriorating hepatic steatosis, and increased visceral and subcutaneous fat volume on the second CT in December 2004 (Fig. 1B). Metformin treatments in combination with high doses of insulin and pioglitazone recovered L/S ratio to 1.18 and decreased the subcutaneous fat volume on the third CT in July 2005 (Fig. 1C). SFA: subcutaneous fat area, VSA: visceral fat area.

glycemic control was resistant to insulin therapy. Afterwards she interrupted insulin therapy. Her family history was unremarkable and there was no history of diabetes in her relatives. Her father's body height was 170 cm and his body weight was 63 kg. Her mother's body height was 153 cm and her body weight was 52 kg. Laboratory data is shown in Table 1. Fasting plasma glucose (FPG) levels were as high as 200 mg/dl, and hemoglobin A1c (HbA1c) was 10.6%. Fasting levels of immuno-reactive insulin (FIRI) increased to 10.1 μ U/ml, the post-prandial level of IRI was 26.9 μ U/ml, urinary C-peptide (CPR) increased to 135 μ g/day, and insulin antibody was negative, showing insulin resistance. In an intravenous glucagon infusion study, serum C-peptide levels increased from 2.7 ng/ml to 6.9 ng/ml during 6 min, so residual β cell function was thought to be preserved. Serum aspartate aminotransferase (AST) was 12 IU/l and alanine aminotransferase (ALT) was 12 IU/l, although decreased liver-to-spleen computed tomography (CT) attenuation values (L/S ratio; 1.02) with hepatomegaly were detected on noncontrast CT, showing slightly hepatic steatosis. The serum cholesterol level was 191 mg/dl, high density lipoprotein cholesterol (HDL-C) level was 37 mg/dl, and triglyceride level was 86 mg/dl. Thus, the patient had low serum HDL-C concentrations, but her serum triglyceride concentrations were not high. Endocrinological examinations were unremarkable except for hypoleptinemia and hypoadiponectinemia, suggesting lean body adiposity. Gynecological examinations did not show polycystic ovaries, but the patient had menstrual abnormalities.

Her clinical course is shown in Fig. 2. A 1400-kcal diet was started, along with multiple daily injections of insulin aspart (16, 16, and 12 units immediately before each meal) and insulin glargine (34 units at bedtime), which was followed by a decrease in HbA1c level from 10.6% to 7.8%,

and an increase in weight from 31 kg to 33.3 kg and in the percentage of body fat (% fat) from 7.5% to 10% in the course of 6 months. Afterwards, we started combination therapy of insulin with pioglitazone (15 mg/day) to enhance insulin sensitivity, which was followed by rather deteriorated glycemic control (up to 8.5% of HbA1c) with 3.3 kg of further weight gain as well as a further 4% fat gain in the course of 12 months. There were no significant changes in serum triglyceride levels, while serum aminotransferase levels and choline esterase (Ch-E) levels increased with a decrease in the L/S ratio to 0.98, suggesting deteriorating hepatic steatosis on the second CT in December 2004. Additionally, visceral and subcutaneous fat volume increased on the second CT (Fig. 1B) with an increase in leptin and adiponectin levels, suggesting improvement of lean body adiposity. We suspected that the disturbances in glycemic control were partly mediated through hepatic insulin resistance via hepatic steatosis. Accordingly, another insulin sensitizer, metformin, was prescribed to improve hepatic insulin sensitivity, producing a slight decrease in serum aminotransferase levels and Ch-E levels. In January 2005, high doses of insulin, up to 98 units per day (16, 16, and 12 units of insulin aspart immediately before each meal and 34 units of insulin glargine at bedtime), along with the maximal dosage (750 mg/day) of metformin were started to control hyperglycemia and improve hepatic insulin sensitivity. Over the following 6 months there were further HbA1c reductions of 1.5% along with a 1.1 kg increase in weight, a further 2% fat gain, and an increase in L/S ratio to 1.18 on the third CT in July 2005 (Fig. 1C).

Discussion

This patient was characterized by reduced fetal growth

Table 1. Laboratory Data

Peripheral blood			Blood chemistry					
WBC	5530	/mm ³	AST	12	IU/l	FPG	198	mg/dl
RBC	491	X10 ⁴ /mm ³	ALT	12	IU/l	HbA1c	10.6	%
Hb	14.7	g/dl	LDH	130	IU/l	FIRI	10.1	μ U/ml
Ht	42.8	%	TP	6.8	g/dl	PIRI	26.9	μ U/ml
PLT	24.1	X10 ⁴ /mm ³	Alb	4.4	g/dl	AcAc	71.4	μ mol/l
Serological tests			Cr	0.3	mg/dl	3OHBA	208.1	μ mol/l
			BUN	21	mg/dl	Leptin	3.6	ng/ml
			UA	3.1	mg/dl	Adiponectin	5	μ g/ml
			Na	137	mEq/l	LH	15.8	mIU/ml
			K	3.8	mEq/l	FSH	10.5	mIU/ml
			Cl	101	mEq/l	Prolactin	6.1	ng/ml
			T-CHO	191	mg/dl	ACTH	22	pg/ml
			HDL-C	37	mg/dl	GH	1.9	ng/ml
TG	86	mg/dl	IGF-1	260	ng/ml			
					17-OHCS	4.4	mg/day	
					17-KS	4.3	mg/day	

GAD: Glutamic acid decarboxylase, U-CPR: urinary C-peptide immuno-reactivity, FIRI: Fasted immuno-reactive insulin, PIRI: Postprandial immuno-reactive insulin, AcAc: Acetoacetate, 3OHBA, 3-Hydroxybutyric acid, LH: Luteinizing hormone, FSH: Follicle stimulating hormone, ACTH: Adrenocorticotrophic hormone, GH: Growth hormone, IGF-1, Insulin-like growth factor-1, 17-OHCS: 17-hydroxycorticosteroids, 17-KS: 17-ketosteroid

despite her maternally healthy pregnancy, no history of rapid “catch-up” growth or total body adiposity rebound, despite a nutrient-rich postnatal life in prepubertal childhood, and adolescent onset insulin-resistant diabetes associated with lean body adiposity without family history of diabetes and lipodystrophies. Lipodystrophy can be either congenital or acquired, and is classified as either complete or partial in distribution (6). The condition described best resembles a form of generalized lipodystrophy, including the lack of fat, insulin resistance and hyperglycemia, and fatty liver. Different viral infections, thyroid dysfunction, and pregnancy have been implicated in the etiology of generalized lipodystrophy. We could not analyze mutations in the insulin receptor gene and abnormal insulinemia, but there were no clear participating factors in this patient because of lack of genetic inheritance.

The Barker hypothesis of fetal programming for adult cardiovascular and metabolic diseases has attracted much interest over the past few years (1). These observations have led to the “thrifty phenotype” hypothesis, which suggests that down-regulation of fetal metabolic pathways is a useful adaptation in response to undernutrition, but, if adult nutrition improves, the ability of the pancreas to maintain homeostasis is exceeded, resulting in diabetes (2-4). However, the present case was not consistent with the “thrifty phenotype” hypothesis, because there was no history of rapid “catch-up” growth or total body adiposity rebound, despite a nutrient-rich postnatal life in prepubertal childhood. Our case strongly suggests that reduced fetal growth might be linked to some fetal genetic factors determining insulin sensitivity and lipogenesis, leading to the later development of diabetes, rather than intrauterine environment. Because insulin is a fetal growth factor and plays an important role in lipo-

genesis, some fetal genetic defects determining insulin sensitivity might induce lower birth weight and lean body adiposity as well as later insulin-resistant diabetes, just as mutations in the glucokinase gene and insulin receptor gene produce reduced fetal growth and insulin resistance. Accordingly, insulin resistance associated with lean body adiposity may play a central role in the pathogenesis of reduced fetal growth as well as later development of type 2 diabetes in this case.

We assessed whether insulin sensitizers, the thiazolidinediones (TZDs) and the biguanides, would improve glycemic control and insulin sensitivity, and affect lean body adiposity in this insulin-resistant patient. Interestingly, the patient's responses to pioglitazone and metformin were different. Treatment with pioglitazone was followed by a deterioration of glycemic control, hepatic steatosis as determined by a decrease in the L/S ratio (7) and an increase in serum aminotransferase levels and Ch-E levels, weight gain, and adiposity gain, while treatment with metformin was followed by a partial improvement of glycemic control and hepatic steatosis as determined by an increase in the L/S ratio and a decrease in serum aminotransferase levels, Ch-E levels, and subcutaneous fat volume. Burant et al (8), studying a partially lipodystrophic mouse, concluded that troglitazone effectively treated diabetes, independent of adipose tissue. The TZDs may act by redistributing lipid from muscle and liver to peripheral adipocytes, producing enhanced insulin sensitivity. On the other hand, Chao et al (9), studying severely lipodystrophic A-ZIP/F-1 mice, concluded that adipose tissue is necessary for the antidiabetic effect of the TZDs and rosiglitazone greatly increases the hepatic steatosis of these mice, which may be due to their increased hepatic expression of peroxisome proliferator-activated receptor-

Figure 2. Clinical course. Percentage of body fat (% fat) was measured by the impedance method. Serum concentration of leptin was quantified by ELISA kit (Institute of Immunology Co., Tokyo, Japan), with the normal value of leptin (7.4 ± 3.7 ng/ml) according to the manufacturer's guidelines. Serum concentration of adiponectin was quantified by ELISA kit (Institute of Otsuka Pharmaceutical Co. Ltd, Tokyo, Japan), with the normal range of adiponectin (5-10 μg/ml) according to the manufacturer's guidelines. Ch-E: choline-esterase (normal range, 4250-7250 IU/l).

gamma (PPAR γ), as is true in this case. We speculate that the antidiabetic effect of pioglitazone, but not metformin, may require an optimal volume of adipose tissue, although it is unclear whether the pioglitazone treatment led to an increase in weight and adiposity along with high doses of subcutaneous insulin in the present case. Metformin treatment might suppress hepatic glucose output via improvement of hepatic insulin sensitivity in this patient with hepatic steatosis, because metformin reduces hepatic steatosis in ob/ob mice and humans (10, 11). It is not known exactly what mechanism may be responsible for the difference of efficacy between pioglitazone and metformin treatments, and TZDs and the biguanide treatments deserve further evaluation in this insulin-resistant patient, because high doses of subcutaneous insulin therapy might play a central role in glycemic control and weight gain mostly due to an increase in adiposity.

Another interesting aspect was that a significant increase in leptin and adiponectin levels occurred concomitantly with an increase in body weight and adiposity. Serum leptin concentrations reflect the amount of body fat being reduced in patients with generalized lipodystrophy (12). Adiponectin levels are decreased in some insulin-resistant states, such as obesity, type 2 diabetes (13), and in patients with lipodystrophies (12). Accordingly, hypoleptinemia and hypoadiponectinemia might be related to lean body adiposity and the association with insulin resistance in this case. It is

known that the TZDs inhibit leptin (ob) gene expression in 3T3-L1 adipocytes (14). However, high doses of subcutaneous insulin in combination with pioglitazone resulted in 6.8 kg of weight gain and 8% fat gain, an increase in the leptin level, followed by improvement of menstrual abnormalities; yet, the increase in the leptin level did not affect the eating behavior. Adiponectin production is stimulated by TZDs and may contribute to increased insulin sensitivity (15). On the other hand, circulating adiponectin levels increase after weight loss in humans. Our observation of reduced adiponectin concentrations in this case are not consistent with previous observations in healthy subjects, in which serum adiponectin levels are paradoxically lower in obese subjects. Furthermore, circulating adiponectin levels increased after weight gain. A possible explanation for the paradox in this case is that high doses of subcutaneous insulin in combination with pioglitazone may lead to an increase in visceral adipocytes, a determinant of insulin sensitivity and adiponectin production, as well as subcutaneous adipocytes (16), followed by an increase in the adiponectin level, because it has been proposed that transplantation of adipose tissue may improve metabolic abnormalities by restoring the serum concentration of adiponectin (17). In various mouse models of lipodystrophy, metabolic abnormalities ameliorate with administration of leptin and adiponectin (18, 19). Recently, Javor ED et al report the long-term effects of leptin replacement in a cohort of patients with generalized lipodys-

trophy. Leptin led to significant and sustained improvements in glycemia, dyslipidemia, and hepatic steatosis (20, 21). Accordingly, high doses of insulin in combination with the administration of leptin and adiponectin may be a useful therapeutic tool to improve the glycemic control and insulin sensitivity in this case.

In conclusion, the present case suggests that some fetal genetic factors determining insulin sensitivity and lipogenesis just as mutations in the glucokinase gene and insulin receptor gene might be linked to reduce fetal growth as well as the development later of insulin-resistant diabetes. However, future studies should explore the genetic factors.

References

1. Barker DJP, Bull AR, Osmond C, Simmonds SJ. Fetal and placental size and risk of hypertension in adult life. *BMJ* **301**: 259-262, 1990.
2. Phillips DI. Birth weight and the future development of diabetes. A review of the evidence. *Diabetes Care* **21**: B150-155, 1998.
3. Gluckman PD, Hanson MA. Living with the past: evolution, development, and patterns of disease. *Science* **305**: 1733-1736, 2004.
4. Hattersley AT, Tooke JE. The fetal insulin hypothesis: an alternative explanation of the association of low birthweight with diabetes and vascular disease. *Lancet* **353**: 1789-1792, 1999.
5. Eriksson JG, Lindi V, Uusitupa M, et al. The effects of the Pro12 Ala polymorphism of the peroxisome proliferators-activated receptor-gamma 2 gene on insulin sensitivity and insulin metabolism interact with size at birth. *Diabetes* **51**: 2321-2324, 2002.
6. Garg A. Lipodystrophies. *Am J Med* **108**: 143-152, 2000.
7. Iwasaki M, Takada Y, Hayashi M, et al. Noninvasive evaluation of graft steatosis in living donor liver transplantation. *Transplantation* **78**: 1501-1505, 2004.
8. Burant CF, Sreenan S, Hirano K, et al. Troglitazone action is independent of adipose tissue. *J Clin Invest* **100**: 2900-2908, 1997.
9. Chao L, Marcus-Samuels B, Mason MM, et al. Adipose tissue is required for the antidiabetic, but not for the hypolipidemic, effect of thiazolidinediones. *J Clin Invest* **106**: 1221-1228, 2000.
10. Lin HZ, Yang SQ, Chuckaree C, Kuhajda F, Ronnet G, Diehl AM. Metformin reverses fatty liver disease in obese, leptin-deficient mice. *Nat Med* **6**: 998-1003, 2000.
11. Marchesini G, Brizi M, Bianchi G, Tomassetti S, Zoli M, Melchionda N. Metformin in non-alcoholic steatohepatitis. *Lancet* **358**: 893-894, 2001.
12. Haque WA, Shimomura I, Matsuzawa Y, Garg A. Serum adiponectin and leptin levels in patients with lipodystrophies. *J Clin Endocrinol Metab* **87**: 2395-2398, 2002.
13. 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* **20**: 1595-1599, 2000.
14. Kallen CB, Lazar MA. Antidiabetic thiazolidinediones inhibit leptin (ob) gene expression in 3T3-L1 adipocytes. *Proc Natl Acad Sci USA* **93**: 5793-5796, 1996.
15. Phillips SA, Ciaraldi TP, Kong AP, et al. Modulation of circulating and adipose tissue adiponectin levels by antidiabetic therapy. *Diabetes* **52**: 667-674, 2003.
16. Mayerson AB, Hundal RS, Dufour S, et al. The effects of rosiglitazone on insulin sensitivity, lipolysis, and hepatic and skeletal muscle triglyceride content in patients with type 2 diabetes. *Diabetes* **51**: 797-802, 2002.
17. Gavrilova O, Marcus-Samuels B, Graham D, et al. Surgical implantation of adipose tissue reverses diabetes in lipoatrophic mice. *J Clin Invest* **105**: 271-278, 2000.
18. Shimomura I, Hammer RF, Ikemoto S, Brown MS, JL Goldstein. Leptin reverses insulin resistance and diabetes mellitus in mice with congenital lipodystrophy. *Nature* **401**: 73-76, 1999.
19. Yamauchi T, Kamon J, Waki H, et al. The fat-derived hormone adiponectin reverses insulin resistance associated with both lipodystrophy and obesity. *Nat Med* **7**: 941-946, 2001.
20. Javor ED, Cochran EK, Musso C, Young JR, Depaoli AM, Gorden P. Long-term efficacy of leptin replacement in patients with generalized lipodystrophy. *Diabetes* **54**: 1994-2002, 2005.
21. Javor ED, Ghany MG, Cochran EK, et al. Leptin reverses nonalcoholic steatohepatitis in patients with severe lipodystrophy. *Hepatology* **41**: 753-760, 2005.