

Metreleptin Supplementation for Improving Lipid and Glycemic Profiles in Acquired Diabetes Lipodystrophy: A Case Report

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Most childhood cancer survivors who undergo hematopoietic stem cell transplantation subsequently develop impaired glucose tolerance and hypertriglyceridemia. These conditions are presumably associated with total-body irradiation-related acquired lipodystrophy and may lead to cardiovascular disease. Metreleptin (recombinant leptin) may help improve the lipoprotein profile, insulin sensitivity, and quality of life of patients with total-body irradiation-related lipodystrophy. This report describes the safe and effective use of metreleptin supplementation for insulin resistance and dyslipidemia in acquired incomplete lipodystrophy.

A 24-year-old Japanese woman with diabetes mellitus and hypertriglyceridemia was admitted to our hospital. She was diagnosed with acute lymphocytic leukemia at 3 years of age and had undergone systemic chemotherapy and total-body irradiation before allogeneic stem cell transplantation. She was also diagnosed with hypertriglyceridemia and diabetes mellitus at 11 years of age. She had a low adiponectin level, low-normal leptin level, and diabetes mellitus with marked insulin resistance. Thus, acquired incomplete lipodystrophy was diagnosed. Her serum triglyceride and lipoprotein profiles improved within 1 month of treatment initiation. Glycemic metabolism and insulin sensitivity in the skeletal muscles improved after 6 months.

As previously reported, metreleptin therapy is effective in improving lipid and glycemic profiles in generalized lipodystrophy. In the present case, we considered that metreleptin supplementation could reduce the remnant VLDL cholesterol fraction and improve diabetes mellitus. We conclude that it may be an effective alternative therapy for improving the expected prognosis of patients with acquired incomplete lipodystrophy, including childhood cancer survivors.

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Abbreviations: AMPK, adenosine monophosphate activated protein kinase; CCS, childhood cancer survivor; IDL, intermediate-density lipoprotein; LPL, lipoprotein lipase.

Childhood cancer survivors (CCSs) often experience impaired glucose tolerance and hypertriglyceridemia as late complications of hematopoietic stem cell transplantation due to total-body irradiation performed during childhood. These patients typically do not have a history of obesity, and they exhibit high-grade insulin resistance, fatty liver, and high mortality from cardiovascular disease [1]. Therefore, such cases are considered to be acquired incomplete lipodystrophy, which is thought to be associated with total-body irradiation and hematopoietic stem cell transplantation [2].

Metreleptin is a recombinant leptin analog and is the only drug indicated specifically for treatment of lipodystrophy, although various therapies are used to treat the related comorbid conditions. Metreleptin has various beneficial effects on metabolic disorders in patients with generalized and incomplete lipodystrophy, particularly those with severe metabolic disorders or low leptin levels [3, 4]. Thus, metreleptin is indicated for treating the complications of leptin deficiency in patients with generalized lipodystrophy [2, 4]. However, the administration of metreleptin as a supplement in patients with incomplete lipodystrophy has not been reported.

We encountered a patient who developed acquired incomplete lipodystrophy, likely caused by total-body irradiation and allogeneic stem-cell transplantation for lymphocytic leukemia. Metreleptin supplementation improved the patient's metabolic disorders and vitality, despite her lipodystrophy-associated long-term diabetes mellitus and hypertriglyceridemia with marked insulin insensitivity. This case suggests that recombinant leptin supplementation might improve the prognosis and quality of life for CCSs with occult incomplete lipodystrophy.

All procedures performed for this patient complied with the ethical standards of the Institutional Review Board of the Kurume University School of Medicine and the 2013 Declaration of Helsinki. The Ethics Committee of Kurume University Hospital approved this report (2019-013), and the patient provided informed consent.

1. Case Presentation

A 24-year-old Japanese woman with hypertriglyceridemia and diabetes mellitus was admitted to our endocrinology center. She had developed acute lymphocytic leukemia at 3 years of age. The treatment involved chemotherapy and total-body irradiation as preparation for allogeneic stem-cell transplantation at 6 years of age. Chronic graft-versus-host disease against the skin and liver developed at 1 month after transplantation, and the patient was treated with prednisolone plus cyclosporine A, followed by mycophenolate mofetil. However, chronic graft-versus-host disease re-emerged at age 11 years as membrane nephropathy, which led to a treatment change from mycophenolate mofetil to prednisolone plus cyclosporine A. She had been receiving insulin (70 U/day in multiple injections) for diabetes mellitus diagnosed at age 11 years. Her hemoglobin A1c and serum triglyceride levels were >10% and >5000 mg/dL, respectively. Treatment with fibrate and pioglitazone was not effective. Her clinical course is shown in an online repository [5].

The laboratory findings before and after metreleptin supplementation are shown in [Table 1](#). Diabetes mellitus with disturbed insulin sensitivity was confirmed on the basis of a low glucose infusion rate of 2.1 mg/kg/min (<5.7 mg/kg/min indicates insulin resistance) as per the euglycemic/hyperinsulinemic glucose clamp method with an insulin infusion dose of 40 mU/m²/min. Although high serum triglyceride levels were detected throughout the day, regardless of dietary intake, her lipoprotein lipase (LPL) activity and apolipoprotein levels were normal. We also detected a high level of free fatty acids, a low adiponectin level, and a low-normal leptin level. The negative results for anti-islet antibodies and other endocrinological examinations are shown in [Table 1](#) and an online repository [5]. Ultrasonography and MRI revealed a fatty liver and intramuscular fat [5]. CT and MRI did not reveal abnormalities in the buttock or thigh subcutaneous fat [5]. Her blood glucose was not controlled with use of insulin, 70 U/d; metformin, 1000 mg/d; and pioglitazone, 15 mg/d [5].

We initiated metreleptin administration on 20 April 2018, when the patient was 24 years old [5]. Metreleptin administration (initially 0.04 mg/kg daily for 1 week, then 0.08 mg/kg

daily subcutaneous injections) immediately regulated her appetite and reduced her food intake. An examination 1 month after the start of metreleptin supplementation revealed remarkable improvements in her serum lipid profile and vitality (Table 1). She also exhibited reductions in her VLDL cholesterol and intermediate-density lipoprotein (IDL) cholesterol levels, with an increase in LDL cholesterol levels (Fig. 1). After 6 months, insulin sensitivity in the skeletal muscle had improved, based on a glucose infusion rate of 3.8 mg/kg/min, and her blood glucose was controlled without insulin (Table 1) [5]. The patient is actively working to maintain satisfactory glucose and lipid metabolism.

2. Discussion

In the present case, we observed a change in the patient's lipoprotein profile after the start of metreleptin supplementation, with reductions in serum triglycerides, VLDL cholesterol, and IDL cholesterol and elevation of the LDL cholesterol fraction. Severe hypertriglyceridemia

Table 1. Laboratory Findings Obtained Before and After Metreleptin Supplementation for Insulin Resistance and Dyslipidemia in a Patient With Acquired Incomplete Lipodystrophy

Finding	Pretreatment	Posttreatment	Reference Range
Serum chemistry			4.0–5.0
Albumin (g/dL)	4.8	4.6	13–30
Aspartate aminotransferase (IU/L)	43	19	7–30
Alanine aminotransferase (IU/L)	61	26	9–32
γ -glutamyltranspeptidase (IU/L)	86	32	10.0–60.0
Ferritin (ng/mL)	364	77	
Lipid profile (mg/dL)			142–219
Total cholesterol	520	248	65.0–139.0
LDL cholesterol	48	67	40–103
HDL cholesterol	23	24	≤ 7.5
RLP cholesterol	181	76.2	30–149
Triglyceride	3897	1828	
Apolipoprotein (mg/dL)			122–161
A-I	119	94	24.6–33.3
A-II	28.8	32.2	69–105
B	159	122	1.5–3.8
C-II	47.3	22.7	5.4–9.0
C-III	136.1	56.2	> 36
E	> 36	17.5	164–284
Lipoprotein lipase (ng/mL)	188	143 ^a	140–850
Free fatty acid (μ Eq/L)	2003	1113	
Diabetes mellitus profile			73–109
Plasma glucose (mg/dL)	145	116	4.9–6.0
Hemoglobin A1c (%)	9.6	8.1	0.8–2.5
Serum C-peptide (ng/dL)	3.96	4.60	0–74.0
3-OHBA (μ mol/L)	58	71	50.0–100.0
Urinary C-peptide (μ g/d)	39.92	NA	
Glucagon loading test			
Δ C-peptide (ng/dL)	2.92	NA	
Glucose clamp, euglycemic method			
GIR (mg/kg BW/min)	2.1	3.2	
Endocrinology			
Leptin (ng/mL)	10	95.8	2.5–21.8
Adiponectin (μ g/mL)	0.3	0.78	> 4.0
Immunology (U/mL)			
Anti-GAD antibody	< 5.0	NA	< 5.0
Anti-IA-2 antibody	< 0.4	NA	< 0.4

Posttreatment values were measured at 1 mo after starting metreleptin supplementation except where noted. Abbreviations: 3-OHBA, 3-hydroxybutyric acid; GA, glycated albumin; GAD, glutamic acid decarboxylase; IA-2, insulinoma-associated antigen-2; IRI, immunoreactive insulin; NA, not available.

^aMeasured at 6 mo.

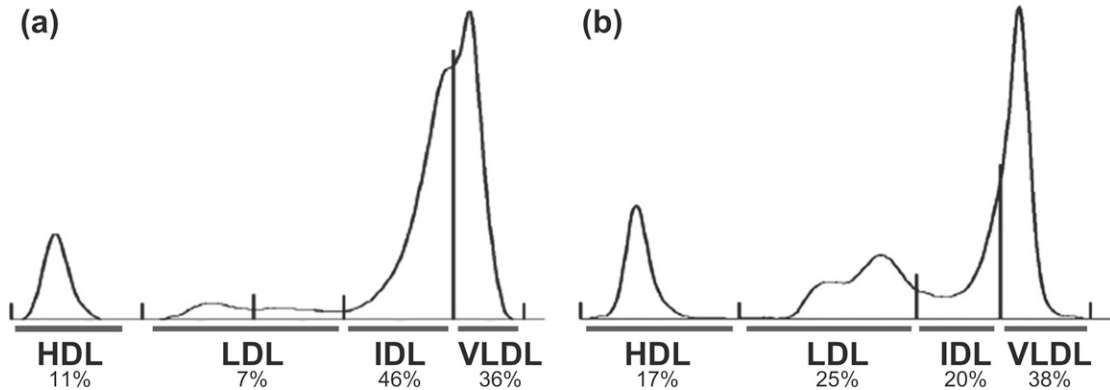


Figure 1. Changing lipoprotein fractions during metreleptin administration in a patient with insulin resistance and dyslipidemia associated with acquired incomplete lipodystrophy. (a) Acrylamide gel electrophoresis revealed a high fraction of VLDL and IDL cholesterol (remnant VLDL) and a low fraction of LDL cholesterol before the metreleptin supplementation. (b) At 1 mo of the metreleptin supplementation, the IDL cholesterol fraction (remnant VLDL) was reduced and the LDL cholesterol fraction was increased.

has been reported in leptin-deficient humans and animals [6], and recombinant leptin replacement reduces plasma and liver levels of triglycerides in patients with generalized lipodystrophy [4]. Reduced fat storage capacity in patients with lipodystrophy and various adipokine deficiencies can lead to VLDL cholesterol overproduction, which manifests as elevated free fatty acid and triglyceride levels [7]. In addition, hyperglycemia and VLDL cholesterol overproduction reduce LPL activity, which explains why lipoprotein fraction abnormalities are observed in patients with generalized lipodystrophy [7]. There are three plausible explanations for how leptin supplementation could improve lipoprotein and triglyceride profiles in patients with partial lipodystrophy. First, high serum triglyceride levels might indicate reduced leptin activity, similar to generalized lipodystrophy. Second, leptin may activate residual brown adipose tissue via the central nervous system [8], which could promote LPL activity and plasma triglyceride clearance. Third, leptin activity may be reduced in atrophic fat tissue after radiation therapy [9], as systemic irradiation therapy can induce abnormalities in adipose tissue differentiation from mesenchymal stem cells [10].

Metreleptin may improve glycemic metabolism in patients with partial lipodystrophy as well as generalized lipodystrophy with undetectable leptin levels [3, 4]. The amelioration of lipotoxicity related to lipid overload via changes in the serum triglyceride and lipoprotein profiles, as well as via reduced lipid accumulation in the liver and muscle tissues, might be a plausible explanation [7]. Furthermore, leptin administration has been shown to increase adenosine monophosphate activated protein kinase (AMPK) activity and significantly reduce triglyceride contents in the liver and skeletal muscle using a lipodystrophy mouse model, which involved low AMPK activity and high fat accumulation in liver. Thus, metreleptin supplementation might improve glucose metabolism and insulin sensitivity by upregulating AMPK activity in a manner distinct from that of metformin [7], even in patients with incomplete lipodystrophy. Therefore, physicians should consider lipodystrophy-related insulin resistance in these cases, although reduced insulin secretion is another essential cause of glucose intolerance.

In conclusion, we encountered a patient with acquired incomplete lipodystrophy that was likely related to total-body irradiation. Metreleptin supplementation improved her serum triglyceride and lipoprotein profiles, with reductions in the VLDL and IDL cholesterol fractions. Furthermore, metreleptin supplementation ameliorated the disturbed insulin sensitivity. These findings suggest that metreleptin supplementation may be a useful alternative therapy for improving metabolic disorders in CCSs.

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