

# Nonobese, Nonketotic Childhood-Onset Diabetes: Look for Lipodystrophies

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**D**iabetes in children and youth poses a unique diagnostic and therapeutic challenge. Although type 1 and type 2 diabetes are undoubtedly the most frequently encountered forms of diabetes, other forms are not uncommon in this age-group. Many young patients with so-called “specific types of diabetes due to other causes” may be misdiagnosed as having type 1 or type 2 diabetes because of a lack of awareness of the various diagnostic possibilities (1). The group of patients with other forms of diabetes constitutes <5% of all patients diagnosed with diabetes before the age of 25 years and includes a variety of conditions (2).

Lipodystrophy, a group of disorders characterized by loss or abnormal distribution of body fat, is associated with insulin resistance and resultant abnormal glucose homeostasis. Depending on the extent of the loss of adipose tissue, these rare disorders are divided into three subgroups: generalized, partial, and localized. Barring the localized form, the other variants are associated with profound metabolic dysfunction. These disorders can be inherited or can be acquired secondary to a number of infectious or immunological diseases and can potentially be associated with diabetes.

Patients with lipodystrophies are often misdiagnosed as having type 2 diabetes and occasionally as having type 1 diabetes. The prevalence of partial lipodystrophy was found to be 0.79% in patients initially misdi-

agnosed as having type 2 diabetes (3). We describe here two patients with childhood-onset diabetes secondary to congenital lipodystrophies and discuss their clinical and diagnostic features.

## Case Presentations

### Case 1

A 6-year-old girl born of a consanguineous union had been detected to have diabetes while undergoing evaluation for failure to gain weight. She was placed on insulin by her primary care physician and referred to us for unsatisfactory glycemic control despite receiving a high dosage of insulin (3.7 units/kg; total daily dose: 52 units). She did not notice osmotic symptoms and had no history of hospitalization. Her birth weight was 2.1 kg, and she had been unusually thin since birth. Her family history was negative for diabetes.

Clinical examination revealed a thin-built girl (weight 14.2 kg, height 1.03 m, BMI 13.3 kg/m<sup>2</sup>) with generalized loss of subcutaneous adipose tissue (Figures 1 and 2). She had hepatomegaly, a small umbilical hernia, and prominent muscles and subcutaneous veins, without acanthosis. Her breasts were of Tanner stage 1, and she had no clitoromegaly. Results of laboratory tests are summarized in Table 1. Ultrasound of the abdomen revealed hepatomegaly with fatty liver and a normal pancreas. MRI scanning showed a loss of subcutaneous fat from the whole body and bone marrow. A whole-body, dual-energy

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■ **FIGURE 1.** Generalized loss of subcutaneous fat with umbilical hernia (Case 1).

X-ray absorptiometry (DXA) scan measured total body fat of 3%.

The patient was treated with three daily injections of short-acting prandial insulin (human regular insulin) and one daily injection of insulin glargine, along with 1.5 g/day of metformin. Her daily insulin require-



■ **FIGURE 2.** Generalized loss of subcutaneous fat with prominent musculature and prominent veins (Case 1).

ments remained high (4.5 units/kg; total daily dose: 64 units), but her blood glucose levels were reasonably controlled after 1 month of therapy.

**Case 2**

A 5-year-old girl was referred from the Department of Hepatology for management of incidentally detected



■ **FIGURE 3.** Acanthosis nigricans over nape of the neck (Case 2).

diabetes while undergoing evaluation for transaminitis. She had been suffering from right upper-abdominal pain and was found to have hepatomegaly and deranged liver function tests. There was no history of increased thirst, polyuria, weight loss, or hospitalization. She had no family history of consanguinity or diabetes in first- or second-degree relatives.

Clinical examination revealed an average-built child with prominent acanthosis (Figure 3). She had loss of subcutaneous fat from the arms, legs, and buttocks with prominent veins, but the subcutaneous fat over her face was preserved (Figures 4 and 5). Results of her laboratory tests are summarized in Table 1. Ultrasound of the abdomen revealed hepatomegaly with fatty liver and a normal pancreas. The girl was put on metformin only with satisfactory glycemic control.

**Questions**

1. What is lipodystrophy?
2. What are the types of lipodystrophy?
3. What are the clinical and biochemical features of lipodystrophy?
4. What is the management of lipodystrophy?

**Commentary**

Adipose tissue is not only a simple storage depot of lipids that provides energy during prolonged fasting, but also plays multiple roles in energy metabolism. Obesity, a condition of generalized increase in adipose tis-



**TABLE 1. Laboratory Data at Presentation**

|                                  | Case 1   | Case 2   |
|----------------------------------|----------|----------|
| Fasting plasma glucose (mg/dL)   | 186      | 156      |
| Postmeal plasma glucose (mg/dL)  | 298      | 272      |
| A1C (%)                          | 9.4      | 8.1      |
| Fasting insulin ( $\mu$ U/mL)    | —        | 62       |
| Triglycerides (mg/dL)            | 258      | 368      |
| HDL cholesterol (mg/dL)          | 32       | 28       |
| Uric acid (mg/dL)                | 7.2      | —        |
| Alanine transaminase (units/L)   | —        | 259      |
| Aspartate transaminase (units/L) | —        | 168      |
| Anti-GAD65 antibody              | Negative | Negative |
| Anti-IA2 antibody                | Negative | Negative |
| Anti-insulin antibody            | Negative | Negative |
| Postmeal C-peptide (ng/mL)       | 6.7      | 8.2      |

IA2, islet antigen 2; GAD, glutamic acid decarboxylase.



■ **FIGURE 4.** Loss of subcutaneous fat from arm with prominent veins (Case 2).



■ **FIGURE 5.** Preserved subcutaneous fat over face (Case 2).

sue mass, is associated with multiple metabolic complications such as diabetes, dyslipidemia, hyperuricemia, and higher cardiovascular morbidity and mortality. Interestingly, the absence or inappropriate reduction of adipose tissue is associated with more severe metabolic complications and early-onset complications (4).

Lipodystrophy predisposes patients to insulin resistance and its associated complications such as acanthosis nigricans, diabetes, hypertriglyceridemia, hepatic steatosis, and polycystic ovaries. The severity of metabolic and other complications depends on the extent of fat loss (5). Metabolic abnormalities observed in this group of patients are also encountered in patients with metabolic syndrome and type 2 diabetes. In fact, type 2 diabetes and the lipodystrophies share a common pathophysiology—a state of defective triglyceride storage in adipose tissue along with ectopic accumulation of lipid in muscles and liver, resulting in insulin resistance and other components of the metabolic syndrome.

Among the inherited forms of lipodystrophies, the most common variants are congenital generalized lipodystrophy (CGL) and familial partial lipodystrophy (FPL). CGL, or Berardinelli-Seip syndrome, is an autosomal recessive disease in which mutation occurs in one of the four genes encoding AGPAT2, seipin, caveolin-1, or PTRF. All of these genes are involved in the proper function of adipose tissue such as adipocyte maturation, lipid storage, formation and maintenance of lipid droplets, membrane composition, DNA repair efficiency, and insulin signaling (6,7).

Seipin mutation is associated with a complete absence of metabolic, bone marrow, and mechanical fat, whereas the other mutations spare the mechanical fat of the orbits, palms, soles, perineum, and periarticular regions. Complete absence of subcutaneous fat gives rise to an emaciated appearance of face and a muscular

appearance of the body. Our patient in Case 1 presented with a loss of subcutaneous fat from the entire body, including her palms and soles, and probably had a seipin mutation.

In the Dunnigan variety of FPL, lipoatrophy typically involves the limbs and the trunk, often accompanied by increased fat deposition in the neck and face, giving rise to a Cushingoid appearance of the face. The Köbberling variety of FPL is characterized by childhood onset, female preponderance, association with type 2 diabetes, and involvement of the limbs and gluteal region (8).

There are no definite diagnostic criteria for lipodystrophies, and a high index of suspicion is of paramount importance. One should carefully look for evidence of subcutaneous fat loss in any nonobese young patient with diabetes, particularly in the presence of acanthosis, hirsutism, hypertriglyceridemia, or fatty liver. Loss of fat from the limbs gives patients a muscular appearance with prominent subcutaneous veins that may be evident at birth in severe cases. The patients in both of the cases presented here had prominent musculature and subcutaneous veins. Imaging modalities such as DXA and MRI scanning are helpful in substantiating the diagnosis, which can be confirmed subsequently by genetic studies.

Patients with lipodystrophy are at high cardiometabolic risk compared to those with more typical type 2 diabetes, and all patients with lipodystrophy should be evaluated with liver function, serum lipid, and hyperuricemia testing at diagnosis. Noninvasive tests for liver fibrosis should also be done. Electrocardiography, Holter monitoring, echocardiography, and stress testing are also advised because of the high prevalence of coronary artery disease, cardiomyopathy, and rhythm disturbances in these patients.

Treatment of lipodystrophies is difficult and focused on reversal of cosmetic disfigurement and

improvement in deranged metabolic parameters. Proper education, which should include both patients and their families, is of utmost importance to allay associated stress and psychological sequelae. Therapeutic lifestyle modification that includes a low-fat diet and regular aerobic physical exercise is crucial. There are no guidelines for drug therapy because of a lack of randomized, controlled trials. However, hypertriglyceridemia should be managed with fibrates or fish oil with or without statins, and diabetes should be managed with metformin, insulin, or both, often in very high doses. The use of thiazolidinediones is controversial and has been incriminated for increased fat deposition in nonlipodystrophic regions (9). Management of disfigurement includes autologous adipose tissue transplantation, implantation of dermal filler in fat deficient areas, and liposuction from areas of unwanted excess adipose tissue.

A major breakthrough in the treatment of lipodystrophies came in 2014 when the U.S. Food and Drug Administration approved metreleptin for use in conjunction with diet to treat patients with congenital generalized or acquired generalized lipodystrophy. Metreleptin is an analog of human leptin made through recombinant DNA technology. Administration of one or two subcutaneous injections of metreleptin daily for 12 months has been associated with significant clinical improvements in a number of studies (10,11). Side effects include fatigue, hypoglycemia, headache, decreased weight, and abdominal pain. Apart from hypersensitivity reactions and infections that may develop in occasional patients, adverse reactions are not severe enough to necessitate drug withdrawal. Development of neutralizing antibody and T-cell lymphoma (in immunodeficient patients) is a major concern related to the widespread use of metreleptin.

**Clinical Pearls**

- Lipodystrophy, a genetically heterogeneous group of disorders characterized by loss or abnormal distribution of adipose tissue and resultant metabolic dysfunction, is not uncommon in diabetes clinics.
- Patients with a working diagnosis of type 1 diabetes who do not have a suggestive or documented history of ketosis and are on a significantly high daily insulin dosage (>2 units/kg/day) should be evaluated thoroughly to establish or refute the primary diagnosis. The presence of partial or complete loss of fat and associated fatty liver, hypertriglyceridemia, low HDL cholesterol, or hyperuricemia is suggestive of lipodystrophy.
- Presence of acanthosis in nonobese young individuals with diabetes should prompt a detailed systemic examination to rule out inherited causes of insulin resistance.

**Duality of Interest**

No potential conflicts of interest relevant to this article were reported.

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