Preface

Lipodystrophy syndromes are a group of metabolic disorders that are either congenital or acquired in onset and are either generalized, partial, or regional in fat loss distribution. They frequently present lipodystrophy-related metabolic derangements or diseases such as marked insulin resistance, diabetes mellitus, hypertriglyceridemia, and nonalcoholic fatty liver disease (NAFLD). Severities are in parallel with the progress of lipodystrophy without correlation with energy intake. No essential therapy has been established to date. However, leptin replacement therapy was approved in 2013, first in Japan and then all over the world, based on its effectiveness and safety in lipodystrophy-related metabolic diseases. Moreover, the Japan Endocrine Society was put in charge of the data on lipodystrophy syndromes by the Ministry of Welfare and Labor of Japan. Since 2015, lipodystrophy syndromes have been designated as “intractable diseases,” and the medical expenses for them are now covered by public health care. Lipodystrophy syndromes are rare diseases because the number of patients with generalized lipodystrophy syndrome is estimated to be around one hundred in Japan. Recently, variant cases of partial lipodystrophy syndrome have been reported in Japan. In 2016, Brown et al. published a report entitled “The Diagnosis and Management of Lipodystrophy Syndromes: A Multi-Society Practice Guideline” in J Clin Endocrinol Metab [1]. In this context, it is necessary to establish criteria to diagnose lipodystrophy syndromes accurately and to determine an indication of the leptin replacement therapy for generalized or partial lipodystrophy syndromes in Japan.

The concept of lipodystrophy syndromes

Lipodystrophy syndromes are either congenital or acquired disorders in their onset, and either generalized, partial, or regional in the extent of fat loss. They present variable lipodystrophy-related metabolic derangements or diseases, such as marked insulin resistance, diabetes mellitus, hypertriglyceridemia, and nonalcoholic fatty
liver disease (NAFLD). The severity of these metabolic abnormalities is in parallel with the progress of lipodystrophy without correlation with energy intake.

In addition to mature adipocytes, the adipose tissue contains preadipocytes, vascular endothelial cells, vascular smooth muscle cells, macrophages, fibroblasts, and adipose tissue-derived mesenchymal stem cells, among others. Fig. 1 presents an electron microscope image of abdominal subcutaneous adipose tissue from a patient with congenital generalized lipodystrophy syndrome due to BSCL2 gene mutation (image provided by the Department of Endocrinology and Metabolism, Kyoto University Hospital). In patients with lipodystrophy syndromes, the number and size of mature adipocytes decrease and the amount of collagen fibers in their adipose tissue increases, compared with those in normal subjects, even if their energy intake is much greater than their energy expenditure.

Lipodystrophy, the atrophy of the adipose tissue is thought to derive from genetic mutations involved in embryogenesis, differentiation, proliferation, and adipocyte function, as well as being triggered by autoimmunity, infections, response to drugs, mechanical compression, denervation, etc. Lipodystrophy syndromes are different from emaciation due to negative energy balance caused by food restriction, excessive exercise, and wasting diseases. They do not improve despite excessive energy intake. Moreover, the extent of lipodystrophy, whether generalized, partial, or regional, is determined by specific causes, which respectively induce those generalized, partial, or regional syndromes.

Adipose tissue has various physiological roles: 1) to store excess energy as lipids and reutilize it when necessary, 2) to secrete adipocytokines (adipokines) as an endocrine organ, 3) to work as a cushion against external shock, 4) to keep the body temperature insulated against external temperature change, among others. In lipodystrophy syndromes, these functions are decreased or lost altogether. As a result, excessive energy that cannot be deposited in atrophic adipose tissue is released into the bloodstream and then stored in non-adipose tissue such as the liver, skeletal muscles, and other organs, resulting in hypertriglyceridemia, insulin resistance, cell damage, and other metabolic dysfunctions. Moreover, leptin, a representative adipokine, which inhibits feeding, decreases in the blood and leads to augmented appetite and increased energy intake. Subsequently, lipodystrophy syndromes frequently lead to metabolic derangements or diseases, such as severe insulin resistance, diabetes mellitus, hypertriglyceridemia, and steatohepatitis (fatty liver).

(Supplement 1) Adipocytes are classified as white, brown, and beige adipocytes, as recently reported in humans. Accumulating evidence indicates that lipodystrophy syndromes are primarily derived from the dystrophy of white adipocytes, although they might also be caused by the dystrophy of brown and beige adipocytes. Further studies are necessary to elucidate the possible lipodystrophy of brown and beige adipocytes in individual cases.

(Supplement 2) Adipose tissue distributes in subcutaneous areas, intra-abdominal and intra-thoracic regions as well as in the bone marrow and retro-orbital regions, although the functions specific for these anatomic locations are unclear.

(Supplement 3) In the present guideline, fat accumulation in adipose tissue is designated as “eutopic fat deposition,” whereas that in non-adipose tissue such as the liver, skeletal muscles, and pancreas is designated as “ectopic fat deposition.”

(Supplement 4) The extent of lipodystrophy is expressed as generalized, partial, or regional, where “partial” means symmetrical distribution, while “regional” indicates non-symmetrical, localized distribution.

**Terminology used**

Although the syndromes are variably named lipodystrophy syndromes, congenital systemic fat development disorder syndromes, and so on, “lipodystrophy syndromes” will be used in the present practice guideline. Also, “lipoatrophic diabetes” will be used to describe diabetes mellitus caused by lipodystrophy syndromes, as is the usual practice.

(Supplement) In the literature, “lipoatrophy” is used to express fat loss, and “lipodystrophy” is used to describe
the abnormal extent of adipose tissue [2]. Since the lipodystrophy concept contains lipatrophy within it, the term “lipodystrophy syndrome” is used in the present guideline. Also, diabetes mellitus complicated with lipodystrophy will be called “lipatrophic diabetes” as is the usual practice, rather than “lipodystrophic diabetes.”

**Classification of lipodystrophy syndromes**

Lipodystrophy syndromes are disorders with variable etiology, onset, extent, and severity. Etiologically they are classified into two main groups, congenital (genetic mutations) or acquired (autoimmunity, infections, drugs, and others), and then into either generalized, partial, or regional subtypes according to the extent of lipodystrophy (Table 1). Lipodystrophy syndromes with comorbidities such as progeroid and autoinflammatory disorders, which present lipodystrophy and characteristic physical signs, have also been recently reported and are classified into lipodystrophy syndromes associated with progeroid and autoinflammatory disorders (Table 1).

**A. Congenital lipodystrophy syndromes**

**A-1. Congenital generalized lipodystrophy (CGL)**

CGL is also called Berardinelli-Seip congenital lipodystrophy (BSCL). In CGL cases, generalized lipodystrophy, or systemic fat loss, is present at birth or infancy. Appetite is generally augmented, and increased insulin resistance, diabetes mellitus, hypertriglyceridaemia, non-alcoholic fatty liver disease (NAFLD), etc. emerge in childhood or later. It is generally hereditary, but certain cases are sporadic. Almost all causative gene mutations are homozygous or compound heterozygous mutations of AGPAT2 (1-acylglycerol-3-phosphate O-acyltransferase 2) [3] or BSCL2 (Berardinelli-Seip congenital lipodystrophy type 2) [4]. More than fifty percent of the patients with BSCL2 are reported to suffer from mental retardation, which might be related to the high expression of Seipin protein coded by the BSCL2 gene in the brain [5, 6]. Also, a few cases with homozygous or compound heterozygous mutations of CAV1 (caveolin 1) [7] or PTHR (polymerase I and transcript release factor) [8] are reported. Cases with PTHR gene abnormality show systemic muscular atrophy and mild metabolic abnormality. According to the order of discoveries for causative gene mutations, the AGPAT2, BSCL2, CAV1, and PTHR gene abnormalities are called CGL1, CGL2, CGL3, and CGL4, respectively. Recently, compound heterozygous gene mutations of PPARG [9] and homozygous mutations of the c-fos promoter region [10] have been reported as causative genes for CGL. Causative genes are likely to be determined in several cases with CGL for which the causes still remain unclear.

**A-2. Familial partial lipodystrophy (FPLD)**

In early infancy, the extent of adipose tissue is normal. By puberty or at puberty, adipose tissue decreases or is absent in the extremities, while adipose tissue in the shoulders and head is conserved or shows compensatory hypertrophy. Metabolic abnormalities such as diabetes mellitus, etc. develop after puberty in many cases. Its occurrence is generally familial. The causative gene of Koebberling syndrome has yet to be identified, but since its cases were among the first reported, it is thus called FPLD1 [11]. Dunnigan syndrome is called FPLD2, and its causative gene is reported to be heterozygous mutations of LMNA (lamin A/C) [12]. Male patients with LMNA mutations show minimal signs of FPLD and mild abnormalities in metabolism, such as diabetes mellitus, etc., compared with female patients [13]. Also, a few cases with heterozygous mutations of PPARG (peroxisome proliferator-activated receptor-gamma) [14], AKT2 (protein kinase B) [15], and PLIN1 (perilipin 1) [16], and homozygous mutations of CIDEc (cell death-inducing DNA fragmentation factor-like factor c) [17] and LIPE (hormone-sensitive lipase) [18] have been reported. There are certain cases with FPLD for which the genetic mutations have yet to be determined, and some cases of FPLD, mainly in the lower extremities, have been reported in Japan [19-21].

**B. Acquired lipodystrophy syndromes**

**B-1. Acquired generalized lipodystrophy (AGL)**

AGL is also called Lawrence syndrome. No apparent lipodystrophy is seen at birth and it is only later that the onset of generalized lipodystrophy will occur. The number of female patients is approximately three times more

### Table 1 Classification of lipodystrophy syndromes

| A. Congenital lipodystrophy syndromes |
|--------------------------------------|
| A-1. Congenital generalized lipodystrophy (CGL) |
| CGL1 (AGPAT2 genetic abnormality) |
| CGL2 (BSCL2/Seipin genetic abnormality) |
| Others |
| A-2. Familial partial lipodystrophy (FPLD) |
| FPLD1 (unknown causative gene) |
| FPLD2 (LMNA genetic abnormality) |
| Others |

| B. Acquired lipodystrophy syndromes |
|-------------------------------------|
| B-1. Acquired generalized lipodystrophy (AGL) |
| B-2. Acquired partial lipodystrophy (APL) |
| B-3. HIV-associated lipodystrophy |
| B-4. Regional lipodystrophy |
| B-5. Other acquired lipodystrophy |

| C. Progeroid and autoinflammatory disorders-associated syndromes |
|---------------------------------------------------------------|
than males [22]. AGL has been reported to be associated with autoimmune disorders such as panniculitis, juvenile dermatomyositis, and juvenile rheumatoid arthritis. Recently, AGL has been complicated with lymphoma (especially peripheral T-cell lymphoma) [23]. Approximately half of the AGL cases have no definite comorbidities [22]. In general, the complications of AGL such as diabetes mellitus, hypertriglyceridemia, and NAFLD are often quite severe.

B-2. Acquired partial lipodystrophy (APL)

APL is also called Barraquer-Simons syndrome. Before adolescence, lipodystrophy appears in the head and neck region, and gradually spreads to the lower body, until the adipose tissue disappears in the upper body. Compensatory fat accumulation in the adipose tissue is often observed in the buttocks and lower extremities. APL is reported to be approximately four times more frequent in females than in males [24]. Although fat loss in upper body progresses, no metabolic abnormalities, including diabetes mellitus, etc. are seen. The pathogenetic mechanism of APL is still unclear, although about 80% of the cases have low serum complement 3 (C3), and some have a C3 nephritic factor, suggesting the possible autoimmune destruction of adipocytes. Moreover, approximately 20% of the cases are associated with membranoproliferative glomerulonephritis [24].

B-3. HIV-associated lipodystrophy (Human immunodeficiency virus-associated lipodystrophy)

Partial lipodystrophy is reported due to the treatment for HIV infection with nucleotide reverse transcriptase inhibitors and protease inhibitors, etc. [25]. HIV-associated lipodystrophy appears in the face and extremities and gradually spreads. Adipose tissue in unaffected areas may have compensatory fat accumulation, such as buffalo hump and increased visceral fat deposition.

B-4. Regional lipodystrophy

Regional lipodystrophy is known to be triggered by acquired causes such as subcutaneous injections of drugs, mechanical compression, operation scars, etc., and shows no lipodystrophy-associated metabolic abnormalities. Infantile abdominal centrifugal lipodystrophy, which is reported to present recessed lesions in the inguinal or axillary regions and their peripheries, belongs to regional lipodystrophy syndrome. It occurs by three years of age, and subsequently spreads centrifugally for several years, sometimes spreading over the entire abdominal and thoracic regions. However, it stops spreading spontaneously by the age of thirteen and tends to heal [26]. Histological examinations demonstrate inflammatory responses in mild grade, recessed subcutaneous fat defect, and panniculitis in the marginal region. Progressive atrophy of the soft tissue and bone in the unilateral face, mainly in the trigeminal nerve-innervated region, is known as progressive facial hemiatrophy (Parry-Romberg syndrome).

B-5. Other types of acquired lipodystrophy

Cases with diencephalon tumors (mostly pilocytic astrocytoma) present generalized lipodystrophy syndrome at birth or infancy [27]. Their clinical features such as glucose and lipid metabolic abnormalities, NAFLD, increased appetite, precocious puberty, etc. varies from case to case. The treatment for diencephalon tumors improves lipodystrophy syndrome. Since some generalized lipodystrophy syndrome cases were diagnosed prior to the detection of diencephalon tumors, clinical follow-up examinations are needed.

A few cases with partial lipodystrophy were reported to occur after bone marrow transplantation [28, 29]. The pathogenetic mechanism for partial lipodystrophy syndrome is speculated to be caused by chemotherapy with cytotoxic agents, whole-body radiation, graft versus host disease (GVHD), etc.

A new group of non-hereditary partial lipodystrophy in extremities has recently been proposed called “partial lipodystrophy of the limbs” (PLL) [30]. Patients with PLL present bilaterally symmetrical lipodystrophy in the extremities, especially in forearms and lower legs, resulting in severe abnormalities in glucose and lipid metabolism such as insulin resistance, glucose intolerance, NAFLD, hypertriglyceridemia, etc. compared with type 2 diabetes mellitus patients with similar physical constitutions.

C. Progeroid and autoinflammatory disorders-associated lipodystrophy

Syndromes with concomitant unique physical signs as well as lipodystrophy are classified into the subgroup of progeroid and autoinflammatory disorders-associated lipodystrophy.

Mandibuloacral dysplasia (MAD)-associated lipodystrophy consisting of generalized or partial lipodystrophy and hypoplasia of mandibular and clavicular bones is reported to be caused by homozygous mutations or compound heterozygous mutations of LMNA [31] or ZMPSTE24 (zinc metalloprotease) [32]. JMP (“Joint contractures, muscle atrophy, microcytic anemia, and panniculitis-induced lipodystrophy”) syndrome, CANDLE (“chronic atypical neutrophilic dermatitis with lipodystrophy and elevated temperature”) syndrome, and Nakajo-Nishimura syndrome, all three of which are known to be hereditary autoinflammatory diseases, are actually identical to each other and are all caused by heterozygous mutations of PSMB8 (proteasome subunit beta type 8) [33].

Heterozygous causative mutations of LMNA in atypical progeroid syndrome and Hutchinson-Gilford progeria
Epidemiology of lipodystrophy syndromes

There is no accurate statistical data on the prevalence of lipodystrophy syndromes, but it is estimated to be one in one to five million in the United States [41]. There have been case reports of approximately 300 to 500 cases of CGL and FPLD, respectively [42, 43]. About 80 cases of AGL have been reported with a male-to-female ratio of 1:3 [42]. About 250 cases of APL have been reported with a male-to-female ratio of 1:4 [42]. More than one hundred thousand HIV-related lipodystrophy cases have been reported in the United States alone [42].

In Japan, the total number of generalized and partial lipodystrophy is estimated to be about 100 cases [44]. Except for HIV-related lipodystrophy, Japan’s prevalence is similar to those in Europe and the United States. Causative genes for Japanese CGL have been reported to be due mostly to mutations in the BSCL2 gene [45]. Among patients with CGL in Japan, CGL2, due to mutations in the BSCL2 gene, has a male-to-female ratio of 1:1, and there is no difference in the male-to-female ratio from the reports in Europe and the United States. Regional characteristics in the prevalence are unclear.

Pathophysiology of lipodystrophy syndromes

The pathogenetic mechanism of generalized lipodystrophy syndrome is shown in Fig. 2. In generalized lipodystrophy syndrome, the function of energy storage in the adipose tissue is attenuated or lost. Therefore, excess energy that cannot be accumulated in the adipose tissue remains in the bloodstream, and is accumulated as lipids in non-adipose tissue such as the liver, skeletal muscles, and pancreas. As a result, hypertriglyceridemia and ectopic fat accumulation such as NAFLD develop at a high rate. Elevation of serum triglyceride levels and ectopic fat accumulation in the liver and skeletal muscles causes insulin resistance, cellular dysfunction, etc.

Ectopic fat accumulation in the pancreas is also thought to cause impaired insulin secretion. Both insulin resistance and impaired insulin secretion can cause diabetes mellitus. The degree of lipid accumulation in the liver complicated with lipodystrophy syndrome is so severe that it has been reported that approximately 80% of the cases progress to nonalcoholic steatohepatitis (NASH) [46, 47]. The persistence of compensatory hyperinsulinaemia caused by insulin resistance is considered to result in acanthosis nigricans, hirsutism, cardiomegaly, skeletal muscle hypertrophy, and polycystic ovary and hyperandrogenemia in female cases. Also, an accelerated growth rate in childhood has been reported. Polycystic ovary, hyperandrogenemia, and hypogonadotropic hypogonadism due to the decrease of leptin, which will be mentioned later, are responsible for menstrual abnormalities in female cases [48]. The function of the adipose tissue as an endocrine organ that secretes adipokines is also attenuated or lost in generalized lipodystrophy syndrome. Among adipokines, a decrease of leptin, which has an anorectic effect, causes hyperphagia. Also, leptin has an effect of increasing insulin sensitivity [49], an effect of reducing ectopic fat accumulation by promoting fatty acid oxidation in skeletal muscles and liver, an antidiabetic effect [50], and an effect of enhancing triglyceride clearance [51]. A decrease in the leptin level is responsible for the aggravation of metabolic disorders associated with lipodystrophy syndrome.

On the other hand, partial lipodystrophy syndrome is considered to have a more complicated pathophysiology than generalized lipodystrophy syndrome. In partial lipodystrophy syndrome, adipose tissue in non-atrophic areas present compensatory hypertrophy. The plasma leptin level ranges from low normal to high normal or abnormally high levels. In such a pathophysiologic condition of partial lipodystrophy syndrome, atrophic sites of the adipose tissue and leptin resistance may be involved in metabolic disorders or diseases. For example, in FPLD, which is characterized by atrophic adipose tissue mainly in the limbs, the glucose and lipid metabolism is usually impaired. However, APL, which is characterized by atrophic adipose tissue mainly in the upper body, the glucose and lipid metabolism is usually preserved. Partial lipodystrophy syndrome with high plasma leptin levels has leptin resistance similar to obesity. The effects of sites and extent of lipodystrophy and leptin resistance on glucose and lipid metabolism must await further studies in partial lipodystrophy syndrome.

Transplantation of the adipose tissue from wild-type mice to A-ZIP/F-1 mice, a generalized lipodystrophy syndrome model, improves abnormal glucose and lipid metabolism [52]. On the other hand, even when the adipose tissue from leptin-deficient ob/ob mouse is
transplanted to A-ZIP/F-1 mice, glucose and lipid metabolism is not ameliorated [53]. Transgenic mice overexpressing leptin in the liver (LepTg) and A-ZIP/F-1 mice were cross-mated to produce doubly-transgenic mice (LepTg/A-ZIPTg) virtually lacking adipose tissue but having elevated leptin levels. The LepTg/A-ZIPTg mice showed markedly improved glucose and lipid metabolism [54]. These reports indicate that absolute leptin deficiency is involved in generalized lipodystrophy syndrome and that leptin replacement may be therapeutically useful in treating metabolic disorders associated with lipodystrophy syndromes. Clinical trials of leptin replacement therapy for patients with lipodystrophy syndromes were conducted. The efficacy and safety of leptin replacement therapy have been demonstrated for generalized lipodystrophy syndromes and partial lipodystrophy syndromes with low normal leptin levels in humans.

**Diagnosis of lipodystrophy syndromes**

When patients with severe insulin resistance, diabetes mellitus, hypertriglyceridemia, and metabolic disorders such as NAFLD are examined, lipodystrophy syndrome is to be suspected and the onset (congenital or acquired) and the extent of lipodystrophy (generalized or partial, regional) should be assessed.

Other diseases that can cause leanness and weight loss should be excluded. The diagnosis is made according to the “Procedure for diagnosis of lipodystrophy syndromes” described below. First, the possibility of progeroid and autoinflammatory syndrome from physical features should be examined. If these diseases are suspected, a mutational analysis of causative genes is performed to make a diagnosis. Next, the time of onset, the site and extent of lipodystrophy, and family history are examined to determine the type of lipodystrophy syndrome. Whole-body MRI T1-weighted imaging and measurement of plasma leptin levels are useful for the diagnosis of lipodystrophy syndromes. In the case of congenital lipodystrophy syndromes, i.e., CGL and FPLD, a mutational analysis of causative genes can confirm the diagnosis.

**Procedure for diagnosis of lipodystrophy syndromes (Fig. 3)**

Exclude other diseases that can cause leanness and weight loss

Exclude other diseases (anorexia nervosa, poorly controlled diabetes mellitus, hyperthyroidism, adrenocortical insufficiency, cancer cachexia, malabsorption syndrome, severe infections, etc.) that can cause leanness and weight loss when an energy balance is negatively inclined due to food restriction, excessive exercise, etc.

Examine the possibility of progeroid and autoinflammatory syndrome

Progeroid and autoinflammatory syndrome are known to develop into generalized or partial lipodystrophy syndromes. With various physical features that match these syndromes, “progeroid and autoinflammatory syndrome”
(Category C), is to be suspected. Definitive diagnosis often requires a mutational analysis of causative genes.

The following shows typical diseases and their physical signs.

- **Hutchinson-Gilford progeria syndrome**: alopecia, prominent eyes, beaked mouth, hypoplasia of the jaw, thin lips, aged skin
- **Neonatal progeroid syndrome**: beaked nose, prominent scalp veins (phlebomegaly)
- **MAD-associated lipodystrophy**: short stature, mandibular hypoplasia, prominent eyes, joint contracture, skin atrophy with pigmentation, alopecia
- **JMP syndrome, CANDLE syndrome, Nakajo-Nishimura syndrome**: pernio-like skin rash on hands and feet, nodular erythema-like skin rash, recurrent myositis, long and clubbed fingers, partial lipodystrophy and muscle atrophy mainly in the face and the upper limbs, flexion contractures of fingers and elbows
- **MDP syndrome**: mandible hypoplasia, clavicle dysplasia, prominent eyes, joint contractures, beaked nose, scleroderma skin, alopecia, mottled hyperpigmentation
- **SHORT syndrome**: hyperextensibility of joints, inguinal hernia, ocular depression, Rieger anomaly (iris thinning/atrophy)
- **Keppen-Lubinsky syndrome**: severe developmental delay, intellectual disability, hypertonia, prominent eyes, microcephaly

When these physical features are not observed, consider the type of lipodystrophy syndrome.

**Examine the time of onset of lipodystrophy**
Assess when the onset of lipodystrophy occurred, and whether lipodystrophy was observed at birth or from infancy, childhood, or adolescence.

**[Cases in which lipodystrophy is observed at birth or from infancy]**

**Consider the possibility of CGL and check for generalized lipodystrophy**
Check the presence or absence of generalized lipodystrophy by physical examination. The following findings can be seen as physical signs of lipodystrophy syndromes.

- **Head and neck**: hollow of eye, cheek, and temple
- **Upper limbs**: phlebomegaly or enlarged veins, prominent muscularity
Lower limbs: phlebomegaly or enlarged veins, prominent muscularity
- Gluteal region: hollow of buttocks, prominent muscularity
- Trunk: phlebomegaly, prominent muscularity

The following findings and symptoms can be seen as physical signs that occur associated with lipodystrophy syndromes.
- Hyperphagia
- Acanthosis nigricans (axillary region, nape, and elbow, etc.)
- Hepatomegaly
- Hirsutism
- Hypogonadism (oligomenorrhea, amenorrhea, virilization, etc.)

MRI T1-weighted imaging is useful to confirm the extent of lipodystrophy. It is desirable to obtain T1-weighted images of the whole body, i.e., trunk (chest and abdomen), upper and lower limbs, and head. MRI T1-weighted images of representative cases are shown in Fig. 4.

Measurement of plasma (or serum) leptin levels is useful to evaluate the degree of lipodystrophy since plasma or serum leptin levels show a highly positive correlation with percent body fat or body fat quantity.

CGL “congenital generalized lipodystrophy” (Category A-1) is to be suspected when physical and imaging examinations detect generalized lipodystrophy, and the

---

**Fig. 4** Examination of lipodystrophy syndromes using whole-body MRI T1-weighted imaging (case presentations)

Adipose tissue reveals a high signal intensity (increased brightness) on MRI T1-weighted images. T1-weighted images at the level of the head, umbilicus, thighs, and soles of a healthy subject are shown in the left-hand column. At the level of the head, adipose tissue is found subcutaneously and in orbits. At the level of the umbilicus, adipose tissue is found subcutaneously and intraperitoneally. At the level of the thighs, adipose tissue is found subcutaneously and in bone marrow. Subcutaneous adipose tissue is also found in the soles. Representative photographs of patients with various lipodystrophy syndromes are shown (images provided by the Department of Endocrinology and Metabolism, Kyoto University Hospital).

Serum leptin concentrations were measured by a highly sensitive ELISA for leptin (Cosmic Corp., Tokyo, Japan). Normal serum concentrations of leptin ranged from 0.6 ng/mL to 8.9 ng/mL in males and from 1.9 ng/mL to 26.6 ng/mL in females.

A CGL case due to BSCL2 gene mutation: female, BMI, 21.2 kg/m², serum leptin, 0.9 ng/mL, HbA1c, 11.4%, HOMA-R, 11.4, triglyceride, 318 mg/dL. Subcutaneous adipose tissue in the head, abdomen, thighs, and soles have disappeared. Furthermore, adipose tissue in the orbits, abdominal cavity, and bone marrow have also disappeared.

An FPLD case due to LMNA gene mutation: female, BMI, 18.8 kg/m², serum leptin, 1.2 ng/mL, HbA1c, 8.9%, HOMA-R, not determined under insulin therapy, triglyceride, 257 mg/dL. Subcutaneous adipose tissue in the abdomen and thighs have disappeared. On the other hand, adipose tissue in the head, orbits, abdominal cavity, bone marrow, and soles are maintained.

A panniculitis-associated AGL case: female, BMI, 15.5 kg/m², serum leptin, 0.6 ng/mL, HbA1c, 10.0%, HOMA-R, 8.4, triglyceride, 1,941 mg/dL. All of the subcutaneous adipose tissue in the head, abdomen, thighs, and soles have disappeared. Furthermore, all of the other adipose tissue, including the orbits, abdominal cavity, and bone marrow, have also disappeared.

An APL case (Barraquer-Simons syndrome): female, BMI, 19.5 kg/m², serum leptin, 2.5 ng/mL, HOMA-R, 1.0, triglyceride, 102 mg/dL. Subcutaneous adipose tissue in the head and abdomen have disappeared. On the other hand, adipose tissue in the orbits, bone marrow, and soles are maintained. Subcutaneous adipose tissue in the thighs show a marked increase, which is consistent with the interpretation of compensatory hypertrophy.
plasma leptin level is lower than the normal range. The patient is diagnosed as CGL when a homozygous mutation or compound heterozygous mutation of a causative gene is detected. In pediatric patients, the possibility of generalized lipodystrophy syndrome associated with diencephalon tumors is also to be kept in mind. The latter is classified as “other types of acquired lipodystrophy” (Category B-5). Since the treatment of diencephalon tumors can improve lipodystrophy syndrome, the presence or absence of such tumors should be investigated minutely using head MRI and other methods.

(Supplement) Since insulin receptor abnormality presents phenotypes similar to CGL, a differential diagnosis is needed. The severity of insulin receptor dysfunction varies depending on the mutation site of the insulin receptor gene. At birth or by infancy, this disease decreases subcutaneous fat and causes severe insulin resistance, acanthosis nigricans, hyperandrogenism, etc. However, this condition often lacks hypertriglyceridemia and NAFLD because of decreased lipid synthesis in the liver [55].

[Cases in which lipodystrophy is observed from childhood or adolescence]

Examine the extent of lipodystrophy (Fig. 4)

Check the presence or absence of lipodystrophy by physical and imaging examinations. When generalized lipodystrophy is observed, and the plasma leptin level is lower than the normal range, AGL “acquired generalized lipodystrophy” (Category B-1) is to be suspected. In the case of AGL, the presence or absence of coexisting diseases (i.e., panniculitis, juvenile dermatomyositis, juvenile rheumatoid arthritis, etc.) should be examined. In pediatric patients, the possibility of pilocytic astrocytoma is also to be kept in mind (see section “4.” above).

When the extent of lipodystrophy presents a symmetrical pattern, partial lipodystrophy syndrome is to be suspected. When the extent of lipodystrophy is limited to an asymmetrical pattern, “regional lipodystrophy” (Category B-4) is to be suspected. In cases of regional lipodystrophy, pathogenetic causes of lipodystrophy, such as subcutaneous injections of drugs, history of surgery, mechanical compression, etc., are to be examined. In the case of lipodystrophia centrifugalis abdominalis infantilis, the extent and progress of lipodystrophy, skin findings, etc. are helpful.

Examine the family history of partial lipodystrophy syndromes

Examine the family history and when there is family history of partial lipodystrophy, FPLD “familial partial lipodystrophy” (Category A-2) is to be suspected. The patient is diagnosed as FPLD when a heterozygous mutation of a known causative gene or a homozygous mutation, or a compound heterozygous mutation of causative genes is detected. In male cases due to an LMNA gene mutation, lipodystrophy is inconspicuous and metabolic disorders such as diabetes mellitus are so mild that the family history of lipodystrophy syndromes could easily be overlooked and might be determined to be absent. Mutational analysis of causative genes is necessary when FPLD due to an LMNA gene mutation is suspected from the course.

When family history is absent, consider the history of diseases that cause partial lipodystrophy syndromes.

Examine the past history of diseases that cause partial lipodystrophy

Review the past history and medical treatment. If the patient is infected with HIV or treated with anti-HIV therapeutic drugs, there is a possibility of “HIV-related lipodystrophy” (Category B-3).

Partial lipodystrophy syndrome is also known to develop after bone marrow transplantation. In this case, there is a possibility of “other types of acquired lipodystrophy” (Category B-5). If neither is found, then examine the extent of lipodystrophy.

Examine the site of partial lipodystrophy

When bilaterally symmetrical lipodystrophy is found only in the upper body, APL “acquired partial lipodystrophy syndrome” (Category B-2) is to be suspected. In APL, the adipose tissue in the buttocks and lower extremities often present compensatory hypertrophy, and have a complication with membranoproliferative glomerulonephritis reported in about 20% of the cases. When bilaterally symmetrical partial lipodystrophy is found in the limbs, especially in the forearm and calf, “partial lipodystrophy of the limbs” (PLL), which is classified as “other types of acquired lipodystrophy” (Category B-5), is to be suspected.

(Supplement 1) In Japan, a mutational analysis of causative genes for lipodystrophy syndromes is not covered by health insurance.

(Supplement 2) In Japan, the PMDA approved an ELISA for leptin (Cosmic Corp. Tokyo, Japan) as a diagnostic device for generalized lipodystrophy syndrome in 2019, and measurements of serum leptin levels for diagnosis of generalized lipodystrophy syndrome have been covered by health insurance from June, 2021. Measurements of serum leptin levels are useful to evaluate the degree of lipodystrophy since serum leptin levels have a highly positive correlation with percent body fat and body mass index; however, lipodystrophy cannot be diagnosed from serum leptin levels alone because hypoleptinemia is also observed in “leanness” due to causes other than lipodystrophy syndromes. Moreover, patients with plasma leptin levels less than 3.0 ng/mL in male and less than 6.0
ng/mL in female were recruited in a clinical trial of metreleptin replacement therapy for lipodystrophy syndromes in Japan. These criteria may be a useful index for selecting patients with lipodystrophy syndromes for metreleptin therapy.

**Treatment of lipodystrophy syndromes**

At present, no curative therapy has been established for lipodystrophy syndromes. Therefore, current treatments of lipodystrophy syndromes are principally aimed at ameliorating metabolic derangements or diseases arising from lipodystrophy. When necessary, plastic surgical approach is also to be considered.

**Treatment of metabolic derangements or diseases arising from lipodystrophy (Fig. 5)**

Diet therapy and exercise therapy comprise the basis for treating metabolic derangements from lipodystrophy: insulin resistance, diabetes mellitus, hypertriglyceridemia, fatty liver disease, etc. If necessary, pharmacotherapy should be considered. Metreleptin has been newly approved as pharmacotherapy since 2013 in Japan. Leptin replacement therapy by subcutaneous injections of metreleptin ameliorates metabolic derangements or diseases and improves enhanced appetite, as well as corrects disturbances in menstruation in female cases.

**Diet therapy and exercise therapy**

Energy intake for the patients with lipodystrophy syndromes should be decided based on 25–35 kcal/kg \times \text{standard body weight (kg)} as calculated from the patient’s height, with age, sex, and physical activity also taken into account. However, in growing children, care is needed not to limit energy intake by taking into account albumin or cholinesterase levels and other nutritional indices. In patients with hypertriglyceridemia, restrictions on fat intake should also be necessary. Leptin deficiency leads to enhanced appetite in patients, especially with generalized lipodystrophy syndrome. Nutritional advice based on this notion is of particular importance.

Exercise therapy contributes to improvement of metabolic derangements or diseases by supporting skeletal muscle mass and promoting energy expenditure. In lipodystrophy syndrome, reduced physical endurance due to a lack of sufficient energy storage, inability to maintain adequate body temperature in a cold environment (e.g., swimming), or the development of plantar callus due to a loss of shock-absorbing function of the adipose tissue of the soles has been reported. These potential problems need to be considered when prescribing exercise therapy.

**Pharmacotherapy**

**Antidiabetic and antidyslipidemia medications**

Diabetes mellitus associated with lipodystrophy syndromes (lipostrophic diabetes) is characterized by severe insulin resistance. Therefore, high doses of insulin therapy often fail to achieve favorable glycemic control. Monotherapy with insulin secretagogues such as sulfonyleureas or glinides shows little therapeutic effects. Thiazolidinedione, an insulin sensitizer drug, has been reported to improve hyperglycemia or hypertriglycerideremia in patients with partial lipodystrophy syndromes [56, 57], but not in generalized lipodystrophy syndrome. Similarly, another insulin sensitizer, metformin, has been reported to be efficacious in HIV-associated lipodystrophy, but not in other forms of lipodystrophy syndromes [58, 59]. Alpha-glucosidase inhibitors or sodium-glucose cotransporter 2 (SGLT2) inhibitors** (Added in proof) are expected to exert some glycemic control effects because of their insulin-independent mechanisms of action. Inhibition of glucagon secretion by incretin modulators such as dipeptidyl peptidase-4 (DPP-4) inhibitors or glucagon-like peptide-1 (GLP-1) receptor agonists may improve glycemic control.

Hypertriglycerideremia associated with lipodystrophy has been treated with fibrates and other lipid-lowering drugs such as statins, eicosapentaenoic acid (EPA), or intestinal cholesterol transporter inhibitors, etc., often with difficulty in achieving favorable control.

**Treatment with IGF-1 (insulin-like growth factor 1)**

IGF-1 not only promotes cell growth and differentiation but also exerts a glucose-lowering effect like insulin at higher concentrations. This is believed to be the case because its primary structure is similar to insulin. Efficacy of IGF-1 has been reported in diabetic patients with severe insulin resistance, including lipodystrophy syndromes [60, 61]. Unfortunately, IGF-1 lacks effects on enhanced appetite and harbors potential risks of worsening hypertrophic cardiomyopathy associated with lipodystrophy syndromes through its positive effects on cell growth. Therefore, IGF-1 therapy has not been generally tested for the treatment of lipodystrophy syndromes.

**Leptin replacement therapy (metreleptin therapy)**

Decreased plasma leptin levels have been shown to be causally related to the pathophysiology of lipodystrophy syndromes (see “Pathophysiology of lipodystrophy” section of this guideline). Therefore, leptin replacement therapy is rational and effective in patients with lipodystrophy syndromes with lower than normal plasma leptin concentrations. Furthermore, leptin replacement therapy has been reported to reduce enhanced appetite and ameliorate disturbed menstrual cycles in female cases [48, 62, 63]. Following a doctor-initiated clinical trial within the country, metreleptin, a leptin analog, was approved in
Japan in 2013 to treat metabolic derangements or diseases associated with lipodystrophy. Lipodystrophy syndromes have long been considered as diseases with poor prognosis. This is because of the lack of responsiveness to conventional antidiabetic drugs or lipid-lowering drugs and consequent progression of diabetic complications, acute pancreatitis associated with hypertriglyceridemia, liver cirrhosis originating from NAFLD, and hypertrophic cardiomyopathy. It is expected that the introduction of leptin replacement therapy could improve the overall prognosis of lipodystrophy syndromes. It should be noted, however, that atrophic adipose tissue cannot be restored by leptin replacement therapy.

[Indication of metreleptin therapy]

Patients with lipodystrophy syndromes presenting with metabolic derangements or diseases associated with lipodystrophy (insulin resistance, diabetes mellitus, hypertriglyceridemia, etc.) cannot be adequately controlled by diet and exercise therapy alone.

(Supplement 1) In Japan, both generalized and partial lipodystrophy syndromes are indications of metreleptin therapy. However, in a doctor-initiated clinical trial in Japan, it is necessary to note that patients with lipodystrophy syndromes presenting with plasma leptin of less than 3.0 ng/mL in males and less than 6.0 ng/mL in females were enrolled.

In the United States, metreleptin therapy is only approved for the treatment of generalized lipodystrophy syndrome. In a report comparing the effect of metreleptin therapy in generalized and partial lipodystrophy syndromes, no difference was found in the basal glyco-hemoglobin A1c (HbA1c) and triglyceride levels, while improvements in these metabolic parameters were more profound in generalized compared with partial lipodystrophy syndromes [64]. In a subgroup analysis of 21 partial lipodystrophy patients with 4 ng/mL or higher plasma leptin concentrations, metreleptin therapy did not significantly improve these metabolic parameters. In contrast, partial lipodystrophy patients who presented with HbA1c of 8% or higher or with serum triglyceride levels of 500 mg/dL or higher have been reported to have experienced a significant improvement regardless of plasma leptin levels.

Since adverse events due to the production of neutralizing antibodies against metreleptin have been reported (referred to below), it is valid that generalized lipodystrophy syndrome is the indication of metreleptin therapy. However, it should carefully be decided in partial lipodystrophy syndrome with preserved plasma leptin levels with a thorough review of expected benefits and adverse effects.

(Supplement 2) Efficacy of metreleptin therapy for HIV-associated lipodystrophy syndrome has not been established in Japan.

(Supplement 3) The safety of metreleptin therapy for pediatric patients below 6 years of age has not been established in Japan. However, studies from overseas report the experience of administering metreleptin to children who were 23 months old, 37 months old, and five years old. In these cases, they report that metreleptin therapy could have been continued with improvements in glucose and lipid metabolism, fatty liver, and acanthosis nigricans [65, 66].

(Supplement 4) In patients with NAFLD associated with lipodystrophy syndromes, metreleptin therapy effectively reduced lipid accumulation, but there was no change in fibrosis [46, 47].

[Usage and dosage]

Metreleptin is subcutaneously administered once a day in Japan: 0.04 mg/kg for male patients, 0.06 mg/kg for female patients younger than 18 years of age, or 0.08 mg/kg for female patients of 18 years and older. Administration for the three groups of patients should be initiated at 0.02 mg/kg, 0.03 mg/kg, or 0.04 mg/kg, respectively, and gradually increased to the dose shown above in about one month. The dose should then be adequately decreased as needed based on the efficacy and symptoms.

[Evaluation of effectiveness]

- Improvements in glucose and lipid metabolic parameters (HbA1c, fasting plasma glucose, fasting insulin, HOMA index, liver enzymes, triglyceride level, an imaging study of the fatty liver, etc.)
- Improvements in enhanced appetite
- Improvements in skin findings (acanthosis nigricans, etc.)
- Improvements in gonadal dysfunction

Improvements as shown above will appear as early as two weeks after initiation of metreleptin therapy [62]. Effectiveness should be evaluated no later than two months after initiation of therapy. Discontinuation of therapy needs to be considered when the expected effects are not observed. The effects on enhanced appetite are mainly perceived as increased postprandial satiety (feeling of fullness) [63].

[Adverse effects and cautionary notes]

1) Hypoglycemia has been reported when used in conjunction with other antidiabetic agents, especially insulin or insulin secretagogues. When metreleptin is used with antidiabetic agents, it is necessary to be aware of potential hypoglycemic risk. The reduction of these agents may sometimes be required soon after the initiation of therapy.

2) In an overseas clinical trial, the occurrence of acute pancreatitis after the discontinuation of metreleptin
has been reported in a patient with a history of pancreatitis and hypertriglyceridemia, thus requiring the necessary precautions on our part.

3) Production of neutralizing antibodies against metreleptin has been reported [67]. Although many antibodies produced do not exhibit neutralizing activity, interference with the therapeutic efficacy of metreleptin has been reported by the production of antibodies with neutralizing activity [65]. There is a possibility that the neutralizing antibody produced may attenuate the effect of endogenous leptin along with metreleptin. Therefore, indication for the metreleptin therapy should be carefully deliberated with full consideration as to expected benefits and adverse effects, particularly in patients with partial lipodystrophy syndrome with preserved plasma leptin levels.

4) Lymphoma has been reported in three cases of acquired generalized lipodystrophy syndrome under metreleptin therapy [23]. In two of the cases, patients presented with immunodeficiency and hematopoietic abnormality associated with bone marrow failure before treatment and developed peripheral T-cell lymphoma during metreleptin therapy. In the other case, no abnormality was diagnosed before treatment but the patient developed anaplastic large cell lymphoma. Moreover, lymphoma has been reported in two cases (mycosis fungoides and Burkitt lymphoma) of acquired generalized lipodystrophy syndrome who had not been treated with metreleptin [23]. Acquired generalized lipodystrophy syndrome itself should thus be considered as a risk for T-cell lymphoma. Therefore, the potential development of skin lesions or lymph node swelling should be carefully screened in patients with acquired generalized lipodystrophy syndrome, regardless of metreleptin therapy.

**Treatment for the restoration of adipose tissue atrophy**

No curative therapy has been established for adipose tissue atrophy. Thiazolidinedione, a drug that activates the peroxisome proliferator-activated receptor (PPAR) gamma, a transcription factor of vital importance in adipocyte differentation, induces hypertrophy of adipose tissue in non-atrophic regions of the body. At the same time, it does not affect the atrophied parts [68].

In cases of lipodystrophy syndrome caused by acquired etiology, a therapeutic approach targeted at the etiologic condition, subcutaneous panniculitis, or autoimmune disease may be effective.

As a plastic surgical approach, facioplasty has been performed by autologous transplantation of subcutaneous fat tissue free flap or by implanting silicone or other implants as substitutes for fat tissue. Research on soft tissue expansion using adipose tissue-derived stem cells has recently been undertaken, but evidence is still lacking on the efficacy and safety of such procedures. In partial lipodystrophy syndrome, adipose tissue in non-atrophic regions sometimes present with compensatory hypertrophy. Liposuction or resection of the adipose tissue is sometimes performed to dispose of the excess fat mass.

---

**Fig. 5** Flowchart for the treatment of metabolic derangements or diseases associated with lipodystrophy syndromes

1) To be judged as positive for glucose and lipid metabolic abnormality, if one or more of the below three criteria is met:
   - Insulin resistance (fasting insulin concentration of 30 mg/dL or higher),
   - Diabetes mellitus (fasting glucose concentration of 126 mg/dL or higher and HbA1c of 6.5% or higher, or casual glucose of 200 mg/dL or higher and HbA1c of 6.5% or higher),
   - Hypertriglyceridemia (fasting triglyceride concentration of 200 mg/dL or higher).

2) Cautious observations are necessary to determine whether the lipodystrophy is generalized or partial because of the high incidence of future development of glucose and lipid metabolic abnormalities.

3) Diet therapy and exercise therapy alone may sometimes be effective in ameliorating metabolic derangements or diseases in mild cases. Continuation of diet and exercise therapy is required after the initiation of pharmacotherapy.

4) Effectiveness and safety of metreleptin therapy have been confirmed in patients with plasma leptin concentrations of less than 3.0 mg/dL for males and less than 6.0 mg/dL for females. Safety has not been established for pediatric cases of less than 6 years of age. Indication for metreleptin therapy should be carefully decided with full consideration of expected benefits and risks. Efficacy needs to be evaluated no later than two months after the initiation of therapy, and discontinuation should be considered in cases that show no improvement. The effectiveness of metreleptin therapy has not been established for HIV-associated lipodystrophy syndrome in Japan.

5) The effectiveness of thiazolidinedione has been reported in partial lipodystrophy syndrome.
Supplement on the present situation regarding clinical applications of leptin for lipodystrophy syndromes in Japan

Leptin replacement therapy is approved for partial lipodystrophy syndromes as well as generalized lipodystrophy syndromes since 2013 in Japan [1, 69]. In 2019, a highly sensitive enzyme-linked immunosorbent assay (ELISA) for leptin (Cosmic Corp., Tokyo, Japan), which is more sensitive than a RIA for leptin (Millipore, St. Charles, Missouri, U.S.A.), was approved by the PMDA for the diagnosis of generalized lipodystrophy syndrome [69] and its cost has been covered by health insurance from June, 2021 in Japan. Evidence has accumulated in Japan, which indicates that leptin replacement therapy for partial lipodystrophy syndromes is useful for patients with low-normal serum leptin levels before treatment [69]. These results indicate that generalized lipodystrophy is an absolute leptin deficiency, while partial lipodystrophy is a relative leptin deficiency.

Members of the organizing committee of the practice guideline for lipodystrophy syndromes

Chairperson
Kazuwa Nakao, Professor Emeritus, at Kyoto University, Medical Innovation Center, Kyoto University Graduate School of Medicine

Members:
Internal Medicine Group
Yoshihiro Ogawa, Department of Medicine and Bioregulatory Science, Graduate School of Medical Sciences, Kyushu University, & Department of Molecular Endocrinology and Metabolism, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University

Pediatric Group
Tohru Yorifuji, Pediatric Endocrinology, and Metabolism, Osaka City General Hospital
Mari Satoh, Pediatrics Center, Toho University Omori Medical Center

Acknowledgments
The authors wish to thank the Japan Endocrine Society for selecting lipodystrophy syndromes as one of the Japan Endocrine Society’s clinically important diseases. The authors also wish to thank the patients and their families for participating in this ongoing translational research. This work was supported by a Grant-in-Aid for Scientific Research from the Japanese Ministry of Education, Culture, Sports, Science, and Technology. This work was also supported in part by The Smoking Research Foundation, The Japan Research Foundation for Healthy Aging, and The Hormone Station of Japan. The authors declare no other conflicts of interest.

References
1. Brown RJ, Araujo-Vilar D, Cheung PT, Dunger D, Garg A, et al. (2016) The Diagnosis and management of lipodystrophy syndromes: a multi-society practice guideline. J Clin Endocrinol Metab 101: 4500–4511.
2. Oral EA (2003) Lipoatrophic diabetes and other related syndromes. Rev Endocr Metab Disord 4: 61–77.
3. Agarwal AK, Arioglu E, De Almeida S, Akkoc N, Taylor SI, et al. (2002) AGPAT2 is mutated in congenital generalized lipodystrophy linked to chromosome 9q34. Nat Genet 31: 21–23.
4. Magre J, Delepine M, Khalilouf E, Gedde-Dahl T Jr, Van Maldergem L, et al. (2001) Identification of the gene altered in Berardinelli-Seip congenital lipodystrophy on chromosome 11q13. Nat Genet 28: 365–370.
5. Van Maldergem L, Magre J, Khalilouf TE, Gedde-Dahl T Jr, Delepine M, et al. (2002) Genotype-phenotype relationships in Berardinelli-Seip congenital lipodystrophy. J Med Genet 39: 722–733.
6. Agarwal AK, Simha V, Oral EA, Moran SA, Gorden P, et al. (2003) Phenotypic and genetic heterogeneity in congenital generalized lipodystrophy. J Clin Endocrinol Metab 88: 4840–4847.
7. Kim CA, Delepine M, Boutet E, El Mourabit H, Le Lay S, et al. (2008) Association of a homozygous nonsense
caveolin-1 mutation Berardinelli-Seip congenital lipodystrophy. J Clin Endocrinol Metab 93: 1129–1134.
8. Hayashi YK, Matsuda C, Ogawa M, Goto K, Tominaga K, et al. (2009) Human PTRF mutations cause secondary deficiency of caveolins resulting in muscular dystrophy with generalized lipodystrophy. J Clin Invest 119: 2623–2633.
9. Dyment DA, Gibson WT, Huang L, Bassouyihi H, Hegele RA, et al. (2014) Biallelic mutations at PPARG cause a congenital, generalized lipodystrophy similar to the Berardinelli-Seip syndrome. Eur J Med Genet 57: 524–526.
10. Knebel B, Kotzka J, Lehr S, Hartwig S, Avci H, et al. (2013) A mutation in the c-fos gene associated with congenital generalized lipodystrophy. Orphanet J Rare Dis 8: 119.
11. Kobberling J, Willms B, Kattermann R, Creutzfeldt W (1975) Lipodystrophy of the extremities. A dominantly inherited syndrome associated with lipotrophic diabetes. Humangenetik 29: 111–120.
12. Cao H, Hegele RA (2000) Nuclear lamin A/C R482Q mutation in Canadian kindreds with Dunnigan-type familial partial lipodystrophy. Hum Mol Genet 9: 109–112.
13. Vigouroux C, Magre J, Vantyghem MC, Bourut C, Lascols O, et al. (2000) Lamin A/C gene: sex-determined expression of mutations in Dunnigan-type familial partial lipodystrophy and absence of coding mutations in congenital and acquired generalized lipatrophy. Diabetes 49: 1958–1962.
14. Barroso I, Gurnell M, Crowley VE, Agostini M, Schwabe JW, et al. (1999) Dominant-negative mutations in human PPARgamma associated with severe insulin resistance, diabetes mellitus, and hypertension. Nature 402: 880–883.
15. George S, Rochford JJ, Wolfrum C, Gray SL, Schinner S, et al. (2004) A family with severe insulin resistance and diabetes due to a mutation in AKT2. Science 304: 1325–1328.
16. Gandotra S, Le Dour C, Bottomley W, Cervera P, Giraud P, et al. (2011) Perilipin deficiency and autosomal dominant partial lipodystrophy. N Engl J Med 364: 740–748.
17. Rubio-Cabezas O, Puri V, Murano I, Saudek V, Semple RK, et al. (2009) Partial lipodystrophy and Insulin-resistant diabetes in a patient with a homozygous nonsense mutation in CIDE1. EMBO Mol Med 1: 280–287.
18. Farhan SM, Robinson JF, McIntyre AD, Marroso MG, Ticca AF, et al. (2014) A novel LIPE nonsense mutation found using exome sequencing in siblings with late-onset familial partial lipodystrophy. Can J Cardiol 30: 1649–1654.
19. Iwanishi M, Ebihara K, Kusakabe T, Chen W, Ito J, et al. (2009) Clinical characteristics and efficacy of pioglitazone in a Japanese diabetic patient with an unusual type of familial partial lipodystrophy. Metabolism 58: 1681–1687.
20. Iwanishi M, Ebihara K, Kusakabe T, Harada S, Ito-Kobayashi J, et al. (2012) Premature atherosclerosis in a Japanese diabetic patient with atypical familial partial lipodystrophy and hypertriglyceridemia. Intern Med 51: 2573–2579.
21. Iwanishi M, Ebihara K, Kusakabe T, Washiyama M, Ito-Kobayashi J, et al. (2014) Primary intestinal follicular lymphoma and premature atherosclerosis in a Japanese diabetic patient with atypical familial partial lipodystrophy. Intern Med 53: 851–858.
22. Misra A, Garg A (2003) Clinical features and metabolic derangements in acquired generalized lipodystrophy: case reports and review of the literature. Medicine (Baltimore) 82: 129–146.
23. Brown RJ, Chan JL, Jaffe ES, Cochran E, DePaoli AM, et al. (2016) Lymphoma in acquired generalized lipodystrophy. Leuk Lymphoma 57: 45–50.
24. Misra A, Peethambaram A, Garg A (2004) Clinical features and metabolic and autoimmune derangements in acquired partial lipodystrophy: report of 35 cases and review of the literature. Medicine (Baltimore) 83: 18–34.
25. Carr A (2003) HIV lipodystrophy: risk factors, pathogenesis, diagnosis, and management. AIDS 17 Suppl 1: S141–S148.
26. Imamura S, Yamada M, Yamamoto K (1984) Lipodystrophy centrifugalis abdominis infantilis. A follow-up study. J Am Acad Dermatol 11: 203–209.
27. Patni N, Alves C, von Schnurbein J, Wabitsch M, Tannin G, et al. (2015) A novel syndrome of generalized lipodystrophy associated with pilocytic astrocytoma. J Clin Endocrinol Metab 100: 3603–3606.
28. Rooney DP, Ryan MF (2006) Diabetes with partial lipodystrophy following sclerodermatous chronic graft vs. host disease. Diabet Med 23: 436–440.
29. Adachi M, Asakura Y, Muroya K, Goto H, Kigasawa H (2013) Abnormal adipose tissue distribution with unfavorable metabolic profile in five children following hematopoietic stem cell transplantation: a new etiology for acquired partial lipodystrophy. Clin Pediatr Endocrinol 22: 53–64.
30. Strickland LR, Guo F, Lok K, Garvey WT (2013) Type 2 diabetes with partial lipodystrophy of the limbs: a new lipodystrophy phenotype. Diabetes Care 36: 2247–2253.
31. Simha V, Agarwal AK, Oral EA, Fryns JP, Garg A (2003) Genetic and phenotypic heterogeneity in patients with mandibuloacral dysplasia-associated lipodystrophy. J Clin Endocrinol Metab 88: 2821–2824.
32. Ahmad Z, Zackai E, Medne L, Garg A (2010) Early-onset mandibuloacral dysplasia due to compound heterozygous mutations in ZMPSTE24. Am J Med Genet A 152A: 2703–2710.
33. Agarwal AK, Xing C, DeMartino GN, Mizrahi D, Hernandez MD, et al. (2010) PSMB8 encoding the beta5i proteasome subunit is mutated in joint contractures, muscle atrophy, microcytic anemia, and panniculitis-induced lipodystrophy syndrome. Am J Hum Genet 87: 866–872.
34. Garg A, Subramanyam L, Agarwal AK, Simha V, Levine B, et al. (2009) Atypical progeroid syndrome due to heterozygous missense LMNA mutations. J Clin Endocrinol Metab 94: 4971–4983.
35. Takenouchi T, Hida M, Sakamoto Y, Torii C, Kosaki R, et
al. (2013) Severe congenital lipodystrophy and a progeroid appearance: Mutation in the penultimate exon of FBN1 causing a recognizable phenotype. Am J Med Genet A 161A: 3057–3062.
36. Garg A, Xing C (2014) De novo heterozygous FBN1 mutations in the extreme C-terminal region cause progeroid fibrillinopathy. Am J Med Genet A 164A: 1341–1345.
37. Garg A, Kircher M, Del Campo M, Amato RS, Agarwal AK, et al. (2015) Whole-exome sequencing identifies de novo heterozygous CAV1 mutations associated with a novel neonatal-onset lipodystrophy syndrome. Am J Med Genet A 167A: 1796–1806.
38. Pelosini C, Martinelli S, Ceccarini G, Magno S, Barone I, et al. (2014) Identification of a novel mutation in the polymerase delta 1 (POLD1) gene in a lipodystrophic patient affected by mandibular hypoplasia, deafness, progeroid features (MDPL) syndrome. Metabolism 63: 1385–1389.
39. Dyment DA, Smith AC, Alcantara D, Schwartztenzuber JA, Basel-Vanagaite L, et al. (2013) Mutations in PIK3R1 cause SHORT syndrome. Am J Hum Genet 93: 158–166.
40. Masotti A, Uva P, Davis-Keppen L, Basel-Vanagaite L, Cohen L, et al. (2015) Keppen-Lubinsky syndrome is caused by mutations in the inwardly rectifying K+ channel encoded by KCN6. Am J Hum Genet 96: 295–300.
41. Garg A (2000) Lipodystrophies. Am J Med 108: 143–152.
42. Garg A (2004) Acquired and inherited lipodystrophies. N Engl J Med 350: 1220–1234.
43. Patni N, Garg A (2015) Congenital generalized lipodystrophies new insights into metabolic dysfunction. Nat Rev Endocrinol 11: 522–534.
44. Ebihara K, Kusakabe T, Nakao K (2011) Current State of lipodystrophy syndromes in Japan. J Japan Society for the Study of Obesity 17: 15–20 (In Japanese).
45. Ebihara K, Kusakabe T, Masuzaki H, Hobayashi N, Tanaka T, et al. (2004) Gene and phenotype analysis of congenital generalized lipodystrophy in Japanese: a novel homozygous nonsense mutation in seipin gene. J Clin Endocrinol Metab 89: 2360–2364.
46. Javor ED, Ghany MG, Cochran EK, Oral EA, DePaoli AM, et al. (2005) Leptin reverses nonalcoholic steatohepatitis in patients with severe lipodystrophy. Hepatology 41: 753–760.
47. Safar Zadeh E, Lungu AO, Cochran EK, Brown RJ, Ghany MG, et al. (2013) The liver diseases of lipodystrophy: the long-term effect of leptin treatment. J Hepatol 59: 131–137.
48. Oral EA, Ruiz E, Andewelt A, Sebring N, Wagner AJ, et al. (2002) Effect of leptin replacement on pituitary hormone regulation in patients with severe lipodystrophy. J Clin Endocrinol Metab 87: 3110–3117.
49. Ogawa Y, Masuzaki H, Hosoda K, Aizawa-Abe M, Suga J, et al. (1999) Increased glucose metabolism and insulin sensitivity in transgenic skinny mice overexpressing leptin. Diabetes 48: 1822–1829.
50. Tanaka T, Hidaka S, Masuzaki H, Yasue S, Minokoshi Y, et al. (2005) Skeletal muscle AMP-activated protein kinase phosphorylation parallels metabolic phenotype in leptin transgenic mice under dietary modification. Diabetes 54: 2365–2374.
51. Matsuoka N, Ogawa Y, Masuzaki H, Ebihara K, Aizawa-Abe M, et al. (2001) Decreased triglyceride-rich lipoproteins in transgenic skinny mice overexpressing leptin. Am J Physiol Endocrinol Metab 280: E334–E339.
52. Gavrilova O, Marcus-Samuels B, Graham D, Kim JK, Shulman GI, et al. (2000) Surgical implantation of adipose tissue reverses diabetes in lipodystrophic mice. J Clin Invest 105: 271–278.
53. Colombo C, Cutson JJ, Yamauchi T, Vinson C, Kadowaki T, et al. (2002) Transplantation of adipose tissue lacking leptin is unable to reverse the metabolic abnormalities associated with lipodystrophy. Diabetes 51: 2727–2733.
54. Ebihara K, Ogawa Y, Masuzaki H, Shintani M, Miyana K, et al. (2001) Transgenic overexpression of leptin rescues insulin resistance and diabetes in a mouse model of lipodystrophic diabetes. Diabetes 50: 1440–1448.
55. Semple RK, Sleigh A, Murgatroyd PR, Adams CA, Black L, et al. (2009) Postreceptor insulin resistance contributes to human dyslipidemia and hepatic steatosis. J Clin Invest 119: 315–322.
56. Owen KR, Donohoe M, Ellard S, Hattersley AT (2003) Response to treatment with rosiglitazone in familial partial lipodystrophy due to a mutation in the LMNA gene. Diabet Med 20: 823–827.
57. Ludtke A, Heck K, Genschel J, Mehnert H, Spuler S, et al. (2005) Long-term treatment experience in a subject with Dunnigan-type familial partial lipodystrophy: efficacy of rosiglitazone. Diabet Med 22: 1611–1613.
58. Hadigan C, Corcoran C, Basgoz N, Davis B, Sax P, et al. (2000) Metformin in the treatment of HIV lipodystrophy syndrome: A randomized controlled trial. JAMA 284: 472–477.
59. Sheth SH, Larson RJ (2010) The efficacy and safety of insulin-sensitizing drugs in HIV-associated lipodystrophy syndrome: a meta-analysis of randomized trials. BMC Infect Dis 10: 183.
60. Kuzuya H, Matsuura N, Sakamoto M, Makino H, Sakamoto Y, et al. (1993) Trial of insulin-like growth factor I therapy for patients with extreme insulin resistance syndrome. Diabetes 42: 696–705.
61. Satoh M, Yoshizawa A, Takesu M, Saji T, Yokoya S (2006) Long-term effects of recombinant human insulin-like growth factor I treatment on glucose and lipid metabolism and the growth of a patient with congenital generalized lipodystrophy. Endocr J 53: 639–645.
62. Ebihara K, Kusakabe T, Hirata M, Masuzaki H, Miyana K, et al. (2007) Efficacy and safety of leptin-replacement therapy and possible mechanisms of leptin actions in patients with generalized lipodystrophy. J Clin Endocrinol Metab 92: 532–541.
63. Aotani D, Ebihara K, Sawamoto N, Kusakabe T, Aizawa-Abe M, et al. (2012) Functional magnetic resonance imaging analysis of food-related brain activity in patients with lipodystrophy undergoing leptin replacement therapy. J Clin Endocrinol Metab 97: 3663–3671.
64. Diker-Cohe T, Cochran E, Gorden P, Brown RJ (2015) Partial and generalized lipodystrophy: comparison of baseline characteristics and response to metreleptin. *J Clin Endocrinol Metab* 100: 1802–1810.

65. Beltrand J, Lahlou N, Le Charpentier T, Sebag G, Leka S, *et al.* (2010) Resistance to leptin-replacement therapy in Berardinelli-Seip congenital lipodystrophy: an immunological origin. *Eur J Endocrinol* 162: 1083–1091.

66. Araujo-Vilar D, Sanchez-Iglesias S, Guillin-Amarelle C, Castro A, Lage M, *et al.* (2015) Recombinant human leptin treatment in genetic lipodystrophic syndromes: the long-term Spanish experience. *Endocrine* 49: 139–147.

67. Javor ED, Cochran EK, Musso C, Young JR, Depaoli AM, *et al.* (2005) Long-term efficacy of leptin replacement in patients with generalized lipodystrophy. *Diabetes* 54: 1994–2002.

68. Simha V, Rao S, Garg A (2008) Prolonged thiazolidinedione therapy does not reverse a fat loss in patients with familial partial lipodystrophy, Dunnigan variety. *Diabetes Obes Metab* 10: 1275–1276.

69. Nakao K (2019) Translational science: newly emerging science in biology and medicine—Lessons from translational research on the natriuretic peptide family and leptin —. *Proc Jpn Acad Ser B Phys Biol Sci* 95: 538–567.

**Added in proof: SGLT2 inhibitors are effective for diabetes mellitus, including diabetes mellitus in lipodystrophy syndromes, through an insulin-independent mechanism. (Kawana Y., Imai J., Sawada S., Yamada T., and Katagiri H. 2017. Sodium-glucose cotransporter 2 inhibitor improves complications of lipodystrophy: A case report, Annals of Internal Medicine, 166: 450–451.)**