Abnormal Adipose Tissue Distribution with Unfavorable Metabolic Profile in Five Children Following Hematopoietic Stem Cell Transplantation: A New Etiology for Acquired Partial Lipodystrophy

Masanori Adachi1, Yumi Asakura1, Koji Munoya1, Hiroaki Goto2, and Hisato Kigasawa2

1 Department of Endocrinology and Metabolism, Kanagawa Children’s Medical Center, Yokohama, Japan
2 Department of Hematology and Regenerative Medicine, Kanagawa Children’s Medical Center, Yokohama, Japan

Abstract. We report five consecutive patients who underwent hematopoietic stem cell transplantation (HSCT) to treat leukemia or neuroblastoma early in their lives and later manifested abnormal patterns of adipose tissue distribution. Lipoatrophy was remarkable in the gluteal regions and extremities, whereas subcutaneous fat was preserved in the cheeks, neck, and abdomen. In addition, visceral fat deposition, fatty changes in the liver, and metabolic derangements such as insulin resistance and hypertriglyceridemia were evident. These features resemble Dunnigan-type familial partial lipodystrophy, which is a rare condition caused by LMNA gene mutation. These patients shared a common medical history involving HSCT, including conditioning with total body irradiation (TBI). They also received intensive chemotherapy because of multiple metastases (n = 3), relapse (n = 3), and repetitive HSCT (n = 3). We propose HSCT as a new etiology for acquired partial lipodystrophy and recommend that patients who undergo HSCT with TBI and intensive chemotherapy early in their lives must receive careful observation for the possible development of lipodystrophy and metabolic complications.

Key words: chemotherapy, dyslipidemia, hypertriglyceridemia, insulin resistance, total body irradiation

Introduction

Partial lipodystrophy refers to a pathological and unique fat distribution, characterized by lipoatrophy (loss of adipose tissue) and lipo hypertrophy (abnormal fat accumulation) (1, 2). Metabolic complications such as insulin resistance, diabetes, hypertriglyceridemia, and fatty changes in the liver are additional hallmarks of partial lipodystrophy (1–4).

Familial partial lipodystrophy (FPLD) arises from genetic mutations, including mutations in the LMNA (5–7), PPARγ (8–10), AKT2 (11) and CIDEC (12) genes. Specifically, FPLD caused by a LMNA mutation is referred to as Dunnigan-type FPLD, or FPLD2, and is characterized by lipoatrophy in the extremities and buttocks combined with fat accumulation in the face, neck...
and intra-abdominal areas. Among the acquired forms of partial lipodystrophy, the most prevalent one is highly active antiretroviral therapy (HAART)-associated lipodystrophy syndrome found in HIV-infected individuals (13, 14). Acquired partial lipodystrophy can also develop following viral infection, autoimmune disease or membranous proliferative glomerulonephritis (1).

We treated 5 consecutive patients who had previously undergone hematopoietic stem cell transplantation (HSCT) to treat malignancies at a younger age. These patients, later in their lives, manifested aberrant fat distribution patterns similar to those occurring in patients with FPLD2, as well as severe metabolic abnormalities.

**Case Series**

All the study procedures, including the control subjects in body composition analysis, were reviewed and approved by the ethics committee of Kanagawa Children’s Medical Center. Patients 2, 3, 4, and 5 and the mother of patient 1 provided written informed consent for publication of their facial photographs.

**Patient 1, female, acute myeloid leukemia (AML)**

As a result of an evaluation of walking difficulties and repetitive, febrile episodes, a 1-yr-old girl was diagnosed with AML, classified as M4, with multiple extra-marrow involvements, including the central nervous system. Following successful induction chemotherapy, bone marrow transplantations (BMTs) from her mother were attempted twice, but were rejected. A third allogeneic BMT, with conditioning that included total body irradiation (TBI) of 10 Gy, was successful and resulted in long-term remission. However, the patient developed chemotherapy-related leukoencephalopathy, and suffered from intractable epilepsy. To suppress extensive, chronic, graft-versus-host disease (GVHD) (15), she had received steroid therapy for 3 yr (Table 1).

At 17 yr of age, the patient underwent her first endocrinological evaluation (Table 2) because she was short [130.3 cm, −5.3 SD for Japanese standards (16)] and prepubertal. Subcutaneous fat was rather abundant in her cheeks and neck, which resulted in a moon-face appearance (Fig. 1a). In addition, the patient exhibited remarkable abdominal distension, with an abdominal circumference of 69 cm at the navel level. However, both her extremities and buttocks showed marked reductions in subcutaneous fat tissue (Fig. 1b).

An oral glucose tolerance test (OGTT) showed a diabetic blood glucose pattern with tremendous hyperinsulinism (Fig. 2). Mildly elevated alanine aminotransferase (ALT) (56 IU/L) and γ glutamyl transpeptidase (γ GTP) (387 IU/L) levels were found, and fatty changes in the liver were suspected based on abdominal ultrasonography (US). Dyslipidemia was also evident, with fasting triglyceride (TG) levels of 675 mg/dL, high-density lipoprotein cholesterol (HDL-C) of 39 mg/dL and low-density lipoprotein cholesterol (LDL-C) of 168 mg/dL (Table 3).

A magnetic resonance imaging scan revealed a small pituitary gland, and the patient was found to have GH deficiency, subclinical hypothyroidism (TSH, 5.45 µIU/L; free T4, 0.93 ng/dL), and primary ovarian insufficiency (FSH, 60.9 IU/L) (Tables 1 and 2).

**Patient 2, female, AML**

An 8-yr-old girl was diagnosed with AML (M2) through an evaluation for petechiae and epistaxis. Six mo after the first remission was achieved by chemotherapy, a marrow relapse was found. A BMT from a human leukocyte antigen (HLA)-identical donor was conducted, following conditioning that included TBI of 12 Gy. Chronic GVHD with pneumonitis, joint contractures and liver dysfunction required immunosuppressive treatment lasting more than a decade. She also suffered from right-sided femoral neck necrosis (with an onset at age 12), transient aplastic anemia following a parvovirus infection (at age 13) and multiple hepatic angiomas (at age 17).
### Table 1: Treatment summaries for the original malignancies in the 5 patients

| Pt (sex) | Primary disease (onset) | Chemo-therapy* | Radiation (site) | Transplantation (conditioning#) | Chronic graft-versus-host disease classification and treatment@ | Treatment-related complications |
|----------|-------------------------|----------------|-----------------|---------------------------------|---------------------------------------------------------------|----------------------------------|
| 1 (F)    | AML (1 yr)              | VP-16, Ara-C, MIT, THP-ADR, ACR, VCR, MTX (it), HC (it) | ND               | Failed 2 consecutive allogeneic BMTs (BSF, VP-16, L-PAM) Successful third allogeneic BMT (TBI 10 Gy, ATG, TT) | Extensive (skin, liver) CsA (for 1.5 yr), PSL (for 3 yr) | GH deficiency (untreated), hypothyroidism (treated from age 17 yr), leukoencephalopathy, epilepsy, primary hypogonadism (treated from age 17 yr) |
| 2 (F)    | AML (8 yr)              | VP-16, Ara-C, MIT, IDR, MTX (it), HC (it) | ND               | Unrelated BMT following marrow relapse (TBI 12 Gy, BSF, L-PAM) | Extensive (lung, joint, liver) PSL (for 12 yr), FK-506 (for 12 yr) | Femoral neck necrosis, aplastic anemia, hepatic angioma, hypothyroidism (treated from age 15 yr), primary hypogonadism (treated from age 19 yr) |
| 3 (M)    | ALL (0 yr)              | VCR, THP-ADR, L-ASP, MTX, CPM, Ara-C, 6-MP, PSL, DEX | 18 Gy (cranial)  | 2 consecutive allogeneic BMTs following marrow relapse [ 1) TBI 12 Gy, VP-16, Ara-C, CPM 2) BSF, VP-16, Ara-C, CPM] | Extensive (skin, joint) CsA (for 4 yr), AZA (for 9 yr), PSL (for 12 yr), MTX (for 1 yr) | GH treatment (from age 11 to 17 yr), chronic thyroiditis (no treatment) |
| 4 (M)    | NB (1 yr)               | CPM, VP-16, THP-ADR, CDDP, CBDCA | 23.4 Gy (cranial), 18 Gy (right orbit) | Scheduled PBSCT (TBI 12 Gy, CBDCA, VP-16, L-PAM) | None | Hypothyroidism (treated from age 4 yr), empty sella, GH deficiency (treated from age 14 to 20 yr), hypogonadism (treated from age 18 yr) |
| 5 (F)    | NB (1 yr)               | CPM, VP-16, THP-ADR, CDDP, DTIC, IFM | 19.8 Gy (epigastrium), 30 Gy (right iliac) | 2 consecutive autologous BMTs [1 CBDCA, THP-ADR, L-PAM, 2 CBDCA, VP-16, THP-ADR, CPM], allogeneic BMT following regional and marrow relapse (TBI 12 Gy, TT, VP-16) | Extensive (liver, intestine) FK-506 (for 3 yr), PSL (for 3 yr) | GH deficiency (treated from age 11 to 17 yr), primary hypogonadism (treated from age 15 yr), high-frequency deafness, cataract |

F, female; M, male; ND, not done; it, intrathecal injection; BMT, bone marrow transplantation; PBSCT, peripheral blood stem cell transplantation; rt, right. *Abbreviations for agents: VP-16, etoposide; Ara-C, cytarabine; MIT, mitoxantrone hydrochloride; THP-ADR, tetrahydropyranyladriamycin; ACR, aclacinomycin; VCR, vincristine sulfate; MTX, methotrexate; HC, hydrocortisone; IDR, idarubicin hydrochloride; L-ASP, L-asparaginase; CPM, cyclophosphamide; 6-MP, 6-mercaptopurine; PSL, prednisolone; DEX, dexamethasone; CDDP, cisplatin; CBDCA, carboplatin; DTIC, dacarbazine; IFM, ifosfamide. BSF, busulfan; L-PAM, melphalan; ATG, antithymocyte globulin; TT, Thio-TEPA; CsA, cyclosporin A; FK-506, tacrolimus; AZA, azathioprine.
When the patient was 15 yr old, abnormal fat distribution was ascertained by whole body computed tomography (CT) (Fig. 1c). An OGTT showed a normal blood glucose response but with hyperinsulinism (Fig. 2). Dyslipidemia and fatty changes in the liver were also noticed. An endocrinological evaluation revealed mild hypothyroidism (TSH, 9.28 µIU/mL; free T4, 0.89 ng/dL) with primary hypogonadism (FSH, 217.9 IU/L; E2, 5.6 pg/mL).
Patient 3, male, acute lymphoid leukemia (ALL)

This patient was diagnosed with unclassified ALL at 11 mo of age as a result of an evaluation of petechiae. His first remission was achieved by chemotherapy and 18 Gy cranial radiation. A year later, marrow relapse was found. Following chemotherapy, two consecutive allogeneic BMTs were conducted, with 12 Gy TBI conditioning being provided before the first round of BMT (Table 1).

Chronic GVHD, with major symptoms of joint contractures and scleroderma, was treated with immunosuppressants. In accordance with
Adachi et al.

his wishes, GH treatment was conducted for 6 yr beginning at age 11 despite normal GH secretion. Nevertheless, his final height was 142.4 cm (–4.9 SD).

Thinning of the extremities, due to subcutaneous fat loss, and a moon-face appearance were noticed when the patient was 13 yr old. A whole body CT scan taken at age 19 revealed fatty changes in the liver and an abnormal pattern of subcutaneous fat distribution (Fig. 1c). Dyslipidemia and hyperinsulinism were also evident.

### Table 2: Current status and information relevant to the etiology of lipodystrophy in the 5 patients

| Patient | Current status | At diagnosis of lipodystrophy | Estimated onset of lipodystrophy* (yr) | LMNA mutation |
|---------|----------------|-------------------------------|---------------------------------------|--------------|
|         | Age (yr) | BMI (kg/m²) | Typical fat distribution† | Age (yr) | GH status | Thyroid status | Gonadal status |                     |
| 1       | 18     | 17.7     | +                         | 17      | Deficient | Hypothyroid | Hypogonadal | 11                   | Absent |
| 2       | 21     | 12.2     | +                         | 15      | Sufficient | Hypothyroid | Hypogonadal | 13                   | Absent |
| 3       | 23     | 16.5     | +                         | 19      | Sufficient† | Euthyroid | Eugonadal   | 12                   | Absent |
| 4       | 21     | 18.3     | +                         | 19      | Replacement therapy for 5 yr | Replacement therapy for 15 yr | Replacement therapy for 2 yr | 15                   | ND     |
| 5       | 22     | 14.1     | +                         | 17      | Replacement therapy for 5 yr | Euthyroid |                    | 14                   | Absent |

†, present; BMI, body mass index; ND, not determined. †Typical fat distribution denotes lipoatrophy in the gluteal region and extremities coupled with preserved, or even prominent, subcutaneous fat in the cheeks, neck and abdomen. *Onset of lipodystrophy as deduced from the emergence of an elevated triglyceride level. (For details, refer to the Methods section.) ‡GH treatment was conducted from 11 to 17 yr of age despite normal GH secretion.

![BG (mg/dL)](image1) ![IRI (µU/mL)](image2)  

**Fig. 2.** Results of a 75-g oral glucose tolerance test in the 5 patients. Left panel, blood glucose (BG) response; right panel, insulin response. In the criteria developed by the Japanese Diabetes Society, the diabetic pattern is defined as the fasting blood glucose being higher than 126 mg/dL or the blood glucose level at 120 min being higher than 200 mg/dL. The normal pattern is defined as a fasting blood glucose less than 110 mg/dL and a blood glucose level of less than 140 mg/dL at 120 min.
Patient 4, male, neuroblastoma

A 1-yr-old boy developed exophthalmos and neuroblastoma, originating from the left adrenal, with multiple bone and marrow metastases (stage IVa). Following total resection of the primary lesion, complete remission was obtained by chemotherapy and radiation (whole skull, 23.4 Gy; right orbit, 18 Gy). Eight months after diagnosis, peripheral blood stem cell transplantation (PBSCT) was carried out, with conditioning that included 12 Gy TBI. Since age 4, the patient has been receiving L-thyroxine because of primary hypothyroidism (TSH, 22.0 µIU/mL; free T4, 0.78 ng/dL). At age 14, an evaluation for growth failure revealed severe atrophy of the pituitary gland. At that time, abdominal US demonstrated fatty changes in his liver. After a diagnosis of complete GH deficiency, GH treatment was started. At age 18, testosterone administration was introduced due to primary hypogonadism (LH, 7.6 IU/L; FSH, 26.6 IU/L; testosterone, 51 ng/dL).

At 19 yr of age, abnormal liver function tests, dyslipidemia and a moon-face appearance prompted a metabolic reevaluation. Although the degree of aberrant fat distribution was modest compared with other patients, a CT scan demonstrated increased visceral fat with a markedly fatty liver. A diabetic pattern of blood glucose response was observed in an OGTT, as well as pronounced hyperinsulinism.

Patient 5, female, neuroblastoma

A neuroblastoma, with multiple bone metastases (stage IVa), was diagnosed in a 1-yr-old female during the evaluation of an abdominal mass. Following total removal of the primary tumor and chemotherapy, two consecutive autologous BMTs, without TBI, were performed 3-mo apart. A regional relapse in the right iliac bone, as well as marrow relapse, was found one year later. The patient was treated with an allogeneic BMT, the donor being her 2-locus mismatched sister, following 12 Gy TBI conditioning. Thereafter, complete remission was obtained, and immunosuppressants were withdrawn at age 8.

Partial GH deficiency was diagnosed at age 12, and GH treatment was conducted for 5 yr. The patient also exhibited primary hypogonadism, high-frequency deafness and the presence of cataracts. At around age 17, fatty liver, adipose tissue, HLA type, and medication were considered.
changes in the liver and hypertriglyceridemia developed, followed by a mild, abnormal pattern of subcutaneous fat distribution. An OGTT showed normal blood glucose responses, but with hyperinsulinism.

Methods and Results

Body composition analysis with dual-energy X-ray absorptiometry was performed in patient 1 using a Discovery® A Densitometer (Hologic, Inc., Bedford, MA, USA) in fan beam analysis mode and software version 13.3.0.1 (Fig. 1b). To illustrate fat distribution abnormality clearly, a 25-yr-old obese woman and a 29-yr-old healthy nonobese woman served as controls. In the former, this analysis was carried out as one of the routine medical evaluations for obesity.

Visceral fat area at the 4th lumbar spine level was determined with FatVizCalc® (LISIT Co., Ltd., Tokyo, Japan) using the CT images of each patient (Fig. 1c).

Written informed consent for LMNA gene analysis was obtained from patients 2, 3 and 5 and from the mother of patient 1. Patient-specific gDNA was extracted from a nail specimen, and the common mutations in exons 8 and 11 of the LMNA gene, associated with FPLD2, were studied, as previously described (17). The mutation was absent in these patients (Table 2).

The onset of lipodystrophy is difficult to ascertain because the attending hematologists, as well as the patients themselves, are unaware of fat distribution abnormalities. Because serum triglyceride levels were routinely measured in the patients, we deduced the onset of lipodystrophy based on the timing of emergence of an elevated triglyceride level. As listed in Table 2, lipodystrophy seemed to develop about a decade after HSCT.

Discussion

All the described patients demonstrated a characteristic adipose tissue distribution pattern. Lipoatrophy was remarkable in the gluteal region and extremities, whereas subcutaneous fat was preserved, or even prominent, in the cheeks, neck and abdomen. Visceral fat deposition, as well as fatty changes in the livers of these patients, was also evident. This particular distribution pattern resembles that seen in FPLD2, which is caused by a LMNA gene mutation (1, 2, 5–7). Patients with this rare entity, which has an estimated prevalence of 1 in 15 million individuals (1), manifest a peculiar lipodystrophy after adolescence. In addition, metabolic complications, including insulin resistance, diabetes, hypertriglyceridemia, low HDL cholesterol levels and fatty liver, are prevalent in FPLD2 patients (3, 4). Female patients also have an increased risk for developing polycystic ovary syndrome and infertility (18). Compared with generalized lipodystrophy and other types of partial lipodystrophy, leptin and adiponectin levels in FPLD2 are only modestly decreased (19). However, FPLD2 is unlikely the cause of lipodystrophy in these patients, considering its low prevalence and the absence of LMNA gene mutations in the 4 patients tested.

Our patients and those with FPLD2 share similarities in fat distribution patterns and in metabolic derangements. Pronounced hypertriglyceridemia, coupled with decreased HDL cholesterol levels, was present in the 5 patients; elevated LDL cholesterol, defined as levels above 150 mg/dL, was present in 4 patients. The patients had high homeostasis model assessment ratios (HOMA-Rs), indicating insulin resistance, although acanthosis nigricans was not observed in any patients. Two patients had OGTTs that categorized them into the diabetic pattern according to the criteria developed by the Japanese Diabetes Society (see Fig. 2 legend). The patients with the diabetic pattern were found to have pronounced hyperinsulinemia with a peak insulin level exceeding 700 µIU/mL. In the present cases, the levels of leptin and adiponectin were modestly decreased.

The patients described in this report shared a common medical history that included HSCT.
and conditioning with 10–12 Gy TBI. All of them also received intensive chemotherapy because of the severe nature of their diseases, including widespread metastases (patients 1, 4 and 5) and early relapses (patients 2, 3 and 4), and/or repetitive HSCT (patients 1, 3 and 5). Major surgery, however, was only conducted on those with neuroblastomas. Cranial radiation was performed on only 3 patients.

Based on the above observations, we propose HSCT as a new etiology for acquired partial lipodystrophy. Partial lipodystrophy seems to develop following HSCT, including TBI, especially in conjunction with intensive chemotherapy. This outcome appears to occur irrespective of other interventions such as surgery and cranial radiation. Younger age at the time of HSCT may be of significance, considering that 4 patients received transplants during infancy.

We speculate that TBI and/or intensive chemotherapy may damage the function of adipocytes in the subcutaneous fat, thereby limiting their lipid-storage capacity. This may lead to ectopic deposition of fat in visceral adipose tissue, muscle and liver. This hypothesis is reasonable because adipose tissue fibrosis, and the resultant ectopic lipid accumulation, has been demonstrated in obese individuals (20). Although the mechanism for the characteristic pattern of lipodystrophy is unclear, it may reflect the site-specific adipose tissue functions. In a subset of partial lipodystrophy accompanying glomerulonephritis, differential expression of complementary D by various adipose tissues is considered to cause the different degrees of lipodystrophy among the body (21).

It is essential to consider other potential factors that may be relevant to the development of lipodystrophy. Rooney and Ryan (22) reported a female patient who underwent allogeneic HSCT for relapsed ALL and developed partial lipodystrophy, with overt diabetes, 9 yr later. This patient had GVHD-associated scleroderma, and these authors speculated that there was a causative relationship between partial lipodystrophy and scleroderma. This hypothesis is very intriguing considering that decreased adiponectin levels have been described in systemic sclerodermas with autoimmune origins (23, 24). However, the severity of the GVHD varied among our patients, and scleroderma was present only in patient 3. GVHD was entirely absent in patient 4, who underwent autologous HSCT. Therefore, GVHD and GVHD-related scleroderma may not be a prerequisite but may be a predisposing factor for the development of partial lipodystrophy.

Another factor that should be considered is endocrinopathy. Four patients had endocrinological complications such as GHD, hypothyroidism and hypogonadism (Table 2). Although some of these endocrinopathies had been treated at the time of the investigation, hormone deficiency must be present for a significant period before the initiation of hormonal therapy. At present, endocrinopathy, per se, is not regarded as a definite cause of lipodystrophy (1, 2). However, endocrinological complications may be likely to modify the development and/or progress of lipodystrophy, considering that each hormone has its own receptor in the adipose tissue (25, 26), and the relationship between hormonal deficiency and metabolic complications is well-known (27, 28).

A causative relationship between HSCT and lipodystrophy may be disputed based on the absence of reports other than that of Rooney and Ryan (22). However, in accordance with our proposal, a high incidence of fatty liver was also reported in individuals who have undergone HSCT (29). In addition, radiation therapy, including TBI, is an established risk factor for developing metabolic syndrome (30, 31). Moreover, impaired glucose tolerance and dyslipidemia have been described as late complications following HSCT (32–34). We infer that a substantial number of partial lipodystrophy patients may have gone undiagnosed because careful observations are necessary to detect abnormal fat distribution...
and because lipodystrophy is not a well-known condition, especially among pediatricians.

To clarify the incidence of HSCT-related lipodystrophy, as well as the contributions of GVHD, GVHD-scleroderma and endocrinopathies, further studies are clearly needed. Lipodystrophy appears to develop more than a decade after HSCT. In addition, the progress of lipodystrophy may be slow, considering that the OGTT results did not differ over a 10-yr interval in patient 3 (Table 3). Thus, prospective studies with long observation periods may be needed to clarify the reality of this potentially life-threatening complication in childhood cancer survivors.

**Conclusion**

Five pediatric patients manifesting aberrant fat distribution patterns similar to those observed in FPLD2 patients and severe metabolic abnormalities were described. Patients undergoing HSCT, especially when performed early in their lives and in conjunction with TBI and intensive chemotherapy, warrant careful observation for the potential development of partial lipodystrophy.

**Acknowledgments**

We thank Dr. Kumiko Nozawa and Dr. Noriko Aida, Department of Radiology, Kanagawa Children’s Medical Center, for their valuable assistance in preparing the CT and DEXA images.

**References**

1. Fiorenza CG, Chou SH, Mantzoros CS. Lipodystrophy: pathophysiology and advances in treatment. Nat Rev Endocrinol 2011;7: 137–50. [Medline]
2. Garg A. Acquired and inherited lipodystrophies. N Engl J Med 2004;350: 1220–34. [Medline]
3. Schmidt HH, Genschel J, Baier P, Schmidt M, Ockenga J, Tietge UJ, et al. Dyslipidemia in familial partial lipodystrophy caused by an R482W mutation in the LMNA gene. J Clin Endocrinol Metab 2001;86: 2289–95. [Medline]
4. Lüdtke A, Genschel J, Brabant G, Baudant J, Taupitz M, Koch M, et al. Hepatic steatosis in Dunnigan-type familial partial lipodystrophy. Am J Gastroenterol 2005;100: 2218–24. [Medline]
5. Cao H, Hegele RA. Nuclear lamin A/C R482Q mutation in Canadian kindreds with Dunnigan-type familial partial lipodystrophy. Hum Mol Genet 2000;9: 109–12. [Medline]
6. Speckman RA, Garg A, Du F, Bennett L, Veile R, Arioglu E, et al. Mutational and haplotype analyses of families with familial partial lipodystrophy (Dunnigan variety) reveal recurrent missense mutations in the globular C-terminal domain of lamin A/C. Am J Hum Genet 2000;66: 1192–8. [Medline]
7. Shackleton S, Lloyd DJ, Jackson SN, Evans R, Niermeijer MF, Singh BM, et al. LMNA, encoding lamin A/C, is mutated in partial lipodystrophy. Nat Genet 2000;24: 153–6. [Medline]
8. Barroso I, Gurnell M, Crowley VE, Agostini M, Schwabe JW, Soos MA, et al. Dominant negative mutations in human PPARgamma associated with severe insulin resistance, diabetes mellitus and hypertension. Nature 1999;402: 880–3. [Medline]
9. Hegele RA, Cao H, Frankowski C, Mathews ST, LeffT. PPARG F388L, a transactivation-deficient mutant, in familial partial lipodystrophy. Diabetes 2002;51: 3586–90. [Medline]
10. Agarwal AK, Garg A. A novel heterozygous mutation in peroxisome proliferator-activated receptor-gamma gene in a patient with familial partial lipodystrophy. J Clin Endocrinol Metab 2002;87: 408–11. [Medline]
11. George S, Rochford JJ, Wolfrum C, Gray SL, Schinner S, Wilson JC, et al. A family with severe insulin resistance and diabetes due to a mutation in AKT2. Science 2004;304: 1325–8. [Medline]
12. Rubio-Cabezas O, Puri V, Murano I, Saudek V, Semple RK, Dash S, et al. Partial lipodystrophy and insulin resistant diabetes in a patient with a homozygous nonsense mutation in CIDEC. EMBO Mol Med 2009;1: 280–7. [Medline]
13. Shlay JC, Sharma S, Peng G, Gibert CL, Grunfeld C, Terry Beirn Community Programs for Clinical
Lipodystrophy after stem cell transplant

Research on AIDS (CPCRA), et al. The effect of individual antiretroviral drugs on body composition in HIV-infected persons initiating highly active antiretroviral therapy. J Acquir Immune Defic Syndr 2009;51: 298–304. [Medline]

14. Blümer RM, van Vonderen MG, Sutinen J, Hassink E, Ackermans M, van Agtmael MA, et al. Zidovudine/lamivudine contributes to insulin resistance within 3 months of starting combination antiretroviral therapy. AIDS 2008;22: 227–36. [Medline]

15. Shulman HM, Sullivan KM, Weiden PL, McDonald GB, Striker GE, Sale GE, et al. Chronic graft-versus-host syndrome in man. A long-term clinicopathologic study of 20 Seattle patients. Am J Med 1980;69: 204–17. [Medline]

16. Tanaka T, Yokoya S, Kato N, Ito Y, Tachibana K, Sugihara S, et al. Fundamental concept for the evaluation of Japanese children’s physical constitution. J Jap Pediatr Soc 2011;115: 1705–9 (in Japanese).

17. Vigouroux C, Magré J, Vantyghem MC, Bourut C, Lascols O, Shackleton S, et al. 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 lipodystrophy. Diabetes 2000;49: 1958–62. [Medline]

18. Vantyghem MC, Vincent-Desplanques D, Defrance-Faivre F, Capeau J, Fermon C, Valat AS, et al. Fertility and obstetrical complications in women with LMNA-related familial partial lipodystrophy. J Clin Endocrinol Metab 2008;93: 2223–9. [Medline]

19. Haque WA, Shimomura I, Matsuzawa Y, Garg A. Serum adiponectin and leptin levels in patients with lipodystrophies. J Clin Endocrinol Metab 2002;87: 2395. [Medline]

20. Suganami T, Tanaka M, Ogawa Y. Adipose tissue inflammation and ectopic lipid accumulation. Endocr J 2012;59: 849–57. [Medline]

21. Misra A, Peethambaram A, Garg A. Clinical features and metabolic and autoimmune derangements in acquired partial lipodystrophy: report of 35 cases and review of the literature. Medicine (Baltimore) 2004;83: 18–34. [Medline]

22. Rooney DP, Ryan MF. Diabetes with partial lipodystrophy following sclerodematous chronic graft vs. host disease. Diabet Med 2006;23: 436–40. [Medline]

23. Tomčík M, Arima K, Hulejová H, Kuklová M, Filková M, Braun M, et al. Adiponectin relation to skin changes and dyslipidemia in systemic sclerosis. Cytokine 2012;58: 165–8. [Medline]

24. Masui Y, Asano Y, Shibata S, Noda S, Aozasa N, Akamata K, et al. Serum adiponectin levels inversely correlate with the activity of progressive skin sclerosis in patients with diffuse cutaneous systemic sclerosis. J Eur Acad Dermatol Venereol 2012;26: 354–60. [Medline]

25. Ballesteros M, Leung KC, Ross RJ, lismaa TP, Ho KK. Distribution and abundance of messenger ribonucleic acid for growth hormone receptor isoforms in human tissues. J Clin Endocrinol Metab 2000;85: 2865–71. [Medline]

26. Brent GA. Mechanisms of thyroid hormone action. J Clin Invest 2012;122: 3035–43. [Medline]

27. Corona G, Rastrelli G, Morelli A, Vignozzi L, Mannucci E, Maggi M. Hypogonadism and metabolic syndrome. J Endocrinol Invest 2011;34: 557–67. [Medline]

28. Jørgensen JO, Vestergaard E, Gormsen L, Jessen N, Nørrelund H, Christiansen JS, et al. Metabolic consequences of GH deficiency. J Endocrinol Invest 2005;28: 47–51. [Medline]

29. Tomita Y, Ishiguro H, Yasuda Y, Hyodo H, Koike T, Shimizu T, et al. High incidence of fatty liver and insulin resistance in long-term adult survivors of childhood SCT. Bone Marrow Transplant 2011;46: 416–25. [Medline]

30. Nuver J, Smit AJ, Postma A, Sleijfer DT, Gietema JA. The metabolic syndrome in long-term cancer survivors, an important target for secondary preventive measures. Cancer Treat Rev 2002;28: 195–214. [Medline]

31. Talvensaari KK, Lanning M, Tapanainen P, Knip M. Long-term survivors of childhood cancer have an increased risk of manifesting the metabolic syndrome. J Clin Endocrinol Metab 1996;81: 3051–5. [Medline]

32. Taskinen M, Saarinen-Pihkala UM, Hovi L, Lipsanen-Nyman M. Impaired glucose tolerance and dyslipidaemia as late effects after bone-marrow transplantation in childhood. Lancet 2000;356: 993–7. [Medline]

33. Shalitin S, Phillip M, Stein J, Goshen Y,
Carmi D, Yaniv I. Endocrine dysfunction and parameters of the metabolic syndrome after bone marrow transplantation during childhood and adolescence. Bone Marrow Transplant 2006;37: 1109–17. [Medline]

34. Smedmyr B, Wibell L, Simonsson B, Oberg G. Impaired glucose tolerance after autologous bone marrow transplantation. Bone Marrow Transplant 1990;6: 89–92. [Medline]

35. Nakanishi T, Li R, Liu Z, Yi M, Nakagawa Y, Ohzeki T. Sexual dimorphism in relationship of serum leptin and relative weight for the standard in normal-weight, but not in overweight, children as well as adolescents. Eur J Clin Nutr 2001;55: 989–93. [Medline]

36. Takahara M, Katakami N, Kishida K, Kaneto H, Funahashi T, Shimomura I, et al. Circulating adiponectin levels and their associated factors in young lean healthy Japanese women. J Atheroscler Thromb 2013;20: 57–64. [Medline]

37. Ogawa Y, Kikuchi T, Nagasaki K, Hiura M, Tanaka Y, Uchiyama M. Usefulness of serum adiponectin level as a diagnostic marker of metabolic syndrome in obese Japanese children. Hypertens Res 2005;28: 51–7. [Medline]