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Lipoatrophic Diabetes and Other Related Syndromes

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Millions of Americans are afflicted by obesity and type 2 diabetes mellitus. Obesity is characterized by increased body adiposity and leads to insulin resistance. Paradoxically, some conditions that are characterized by a paucity of fat also cause insulin resistance, namely the syndromes of lipoatrophy (Fig. 1). The resemblance between the metabolic abnormalities of these two extreme states of adiposity emphasizes the importance of fat tissue in energy homeostasis. This review focuses on the syndromes of lipodystrophy and lipoatrophy that are at the lean extreme of the spectrum and which are characterized by near-complete absence of fat.

A Definition of Lipodystrophy, Lipoatrophy, and Lipoatrophic Diabetes

Lipoatrophy syndromes comprise a heterogeneous cluster of disease states having in common a lack of fat tissue [1]. The deficiency of adipose tissue can be partial or generalized, and these abnormalities may be congenital or acquired [1]. The characteristic loss of fat is known as "lipoatrophy" whereas an abnormal distribution of fat is "lipodystrophy". The term "lipoatrophic diabetes" refers to patients who have diabetes mellitus in association with lipoatrophy. It is important to realize that lipodystrophy is a generalized term that encompasses lipoatrophy and other abnormalities of adipose tissue such as lipedema or lipomatosis. In this review, we focus on syndromes characterized primarily by adipocyte deficiencies throughout the body. Although it is important to describe the amount and distibution of adipose tissue, there is also a distinction between the actual insuffiency of adipocytes and preadipocytes that results in metabolic disturbances and those states of total body fat deficiency caused by decreased triglyceride storage. In the latter state, the adipocytes are still basically normal, but are chronically forced to mobilize their stored triglycerides (e.g. under conditions of chronic caloric depletion, intense exercise or increased sympathetic drive [2–5]). In all cases of lipoatrophy there is adipocyte insufficiency and the metabolic consequences are peripheral insulin resistance and hypertriglyceridemia. It is also interesting to note that experimental approaches that completely ablate white adipose tissue lead to the metabolic syndrome regardless of the strategy (see below). These observations underscore the importance of the adipocyte not only as storage site for triglycerides; but also as a cell which is capable of sensing nutrient availability and abundance and responding with signals that play a regulatory role in energy storage and partition.

Mechanisms of Disease

Lipodystrophy and lipoatrophy syndromes are characterized by decreased adipose tissue. The congenital forms demonstrate a reduction in adipose tissue throughout life. The proposed mechanism for these forms of lipodystrophy/lipoatrophy results from defects in adipocyte differentiation and function. In the acquired syndromes there is evidence of normal adipocyte development but then a loss of adipose tissue later in life which implies a mechanism of adipocyte destruction. The reduction of adipocytes may occur via decreased growth and differentiation, increased apoptosis, or enhanced destruction as may occur in autoimmune destruction.

In order to better understand possible etiologies of lipodystrophy/lipoatrophy syndromes, it is important to understand normal adipocyte growth and differentiation (Fig. 2). Normal adipose tissue develops in multiple sites throughout the body from embryonic mesenchymal cells. Over the last decade, there have been great advances in understanding the differentiation program of adipocytes. Precursor cells are committed to adipogenesis through transient expression of certain transcription factors such as the CCAAT/enhancer binding proteins (C/EBPs) and Peroxisome proliferator activating receptors (PPARs) [6]. Other transcription factors are also involved either in activating these key factors or controlling the synthesis

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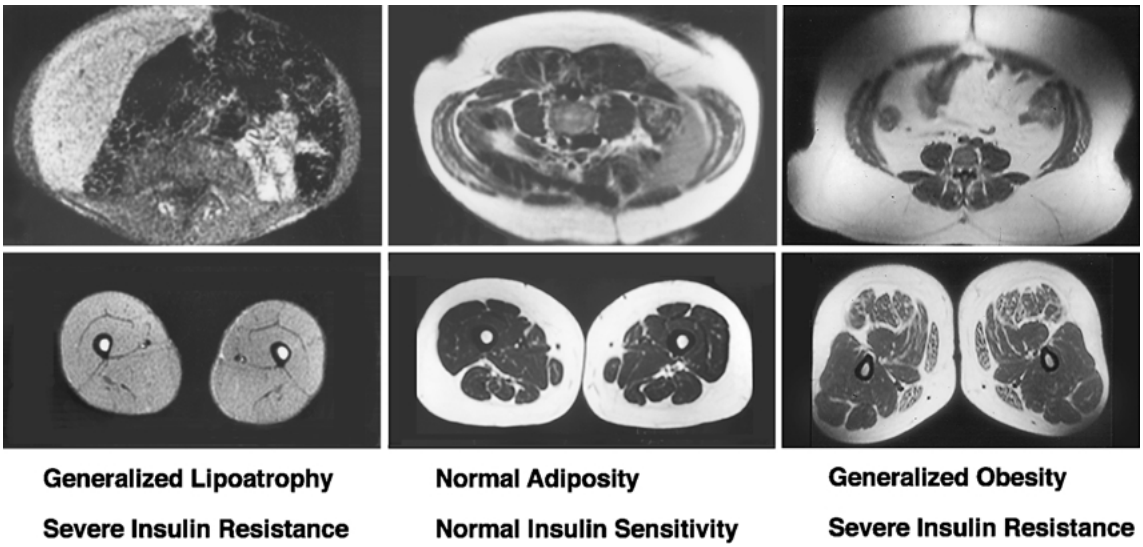

Fig. 1. *Clinical spectrum of adiposity. T1-weighted magnetic resonance images in which lipid appears white. Transverse sections of the torso at the level of the fifth lumbar vertebra (top panels) and mid-thigh (bottom panels) are shown. (Left) Generalized lipoatrophy, (Center) normal individual with body mass index of 24 kg/m^2, (Right) an obese individual with body mass index of 38 kg/m^2. Note the marked absence of all fat depots in the patient with generalized lipoatrophy, with preservation of marrow fat, and a lipid filled liver. Also, the bright color of the muscle is reflective of lipid-filled myocytes.*

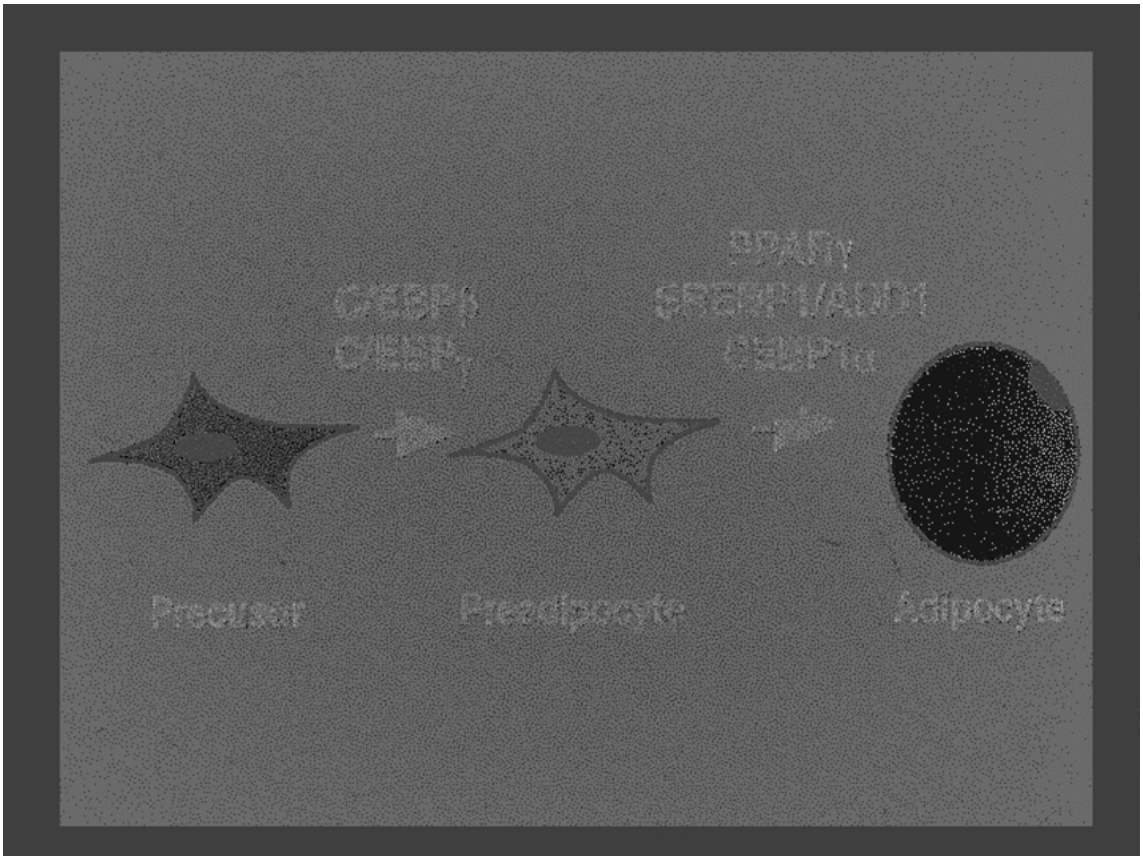

Fig. 2. *Adipocyte diffrentiation. Mesenchymal precursor cells are committed to the adipogenic pathway in an early step that involves transient expression of the transcription factors C/EBP β and δ that leads to the formation of preadipocytes. This is followed by expression of PPARγ, SREBP1/ADD1 and C/EBPα causing the cells to differentiate into mature adipocytes. How the newly discovered lipodystrophy genes fit into this scheme is not yet clear (see text for details). Abbreviations: ADD1, adipocyte determination and diffrentiation-dependent factor 1; C/EBP, CCAAT/enhancer-binding protein; PPAR: peroxisome proliferator-activated receptor; SREBP, sterol regulatory element-binding protein.*

of their ligands (for example sterol regulatory element-binding protein SREBP1/ adipocyte determination and diffrentiation-dependent factor 1 ADD1 may regulate synthesis of ligands for PPARγ [7,8]).

Through expression of these nuclear transcription factors, the cell differentiates into an adipocyte and develops the ability to store triglycerides, repress cell-cycle genes and secrete adipocyte-specific hormones. Recently, a novel molecule called lipin has been cloned as a result of positional cloning efforts to identify the genetic etiology of a naturally occurring mouse model with partial lipoatrophy and fatty liver. This novel protein has nuclear localization and is induced during adipocyte differentiation [9]. Its exact role in the adipocyte differentiation pathway remains to be identified.

Defects in adipocyte differentiation commitment steps may lead to adipocyte deficiency; however, the exact control of normal adipocyte growth and cell cycle are not yet fully understood. Furthermore, as we will discuss later on in this review, identification of some of the genes responsible from known human lipoatrophy syndromes did not easily fit the known pathways in adipocyte differentiation.

Another mechanism by which to lose adipocytes is through increased destruction of these cells (such as induction of apoptosis). Animal models of lipoatrophy have been engineered via either distruption of adipogenesis or induction of adipocyte-death. These models help us understand the pathophysiology of fat loss. Some of these models use an adipose-specific promoter/enhancer to introduce a transgene. A review on animal models of lipoatrophy can be found elsewhere [10].

When discussing the mechanisms of disease in lipoatrophy syndromes, it is important to recognize that the primary event is adipocyte deficiency and that the metabolic problems associated with the syndromes are secondary. The circumstantial evidence for this supposition was based on the similarity of the metabolic phenotype in a wide range of human syndromes. However, the direct proof came with the demonstration that the metabolic phenotype was largely reversed upon fat transplantation in a genetically engineered rodent model of lipoatrophy [11]. Why does fat transplantation reverse metabolic phenotype of lipoatrophy? One hypothesis stresses the endocrine function of the adipocyte. The discovery of the adipocyte hormone leptin underscored the endocrine function of adipose tissue. Leptin communicates body energy stores to the neuroendocrine system to control food-intake and energy expenditure. Leptin has effects (direct or indirect) on the key organs of metabolism, including the liver, muscle and pancreas. Another molecular signal originating from the adipocytes, ACRP 30 [12] (also called adipoQ [13], APM1 or Adiponectin [14]) was found to be important in inducing fat oxidation in the muscle and liver [12]. The list of endocrine signals originating from the adipocyte is likely to increase (see review by Lustig in this issue). Lack of adipocytes results in deficiency of these signals, thus contributing to many of the abnormalities seen in these syndromes characterized by absence of fat. Thus, it is possible to view the metabolic aspects of the lipoatrophy syndromes as a consequence of the hormonal insufficiency created by the absence of the organ producing the hormone.

Classification of Lipoatrophy Syndromes

As mentioned above, absence of fat can be partial or generalized. and the syndrome can manifest at birth or later in life [15]. If fat loss is partial, the residual fat undergoes compensatory hypertrophy. Usually, there is a rough correlation between the severity of metabolic consequences and the degree of fat loss. There is also an entity called focal lipoatrophy where the loss of fat involves a single region in the body. One example of this are the loss of fat in the gluteal area usually following intramuscular injections [16]. Therapy with protein hormones, such as insulin [17,18] and growth hormone [19] may lead to focal lipoatrophy. A focal lipoatrophy may also occur on the face referred to as the Romberg's syndrome [20]. There are other specifically described fat distributions reported in the literature as 'annular" or "semicircular" lipoatrophy [21,22]. Usually, the isolated loss of fat from a limited body region is not associated with metabolic consequences, supporting the hypothesis that a crucial degree of fat loss is required to observe the metabolic abnormalities.

Genetic Syndromes of Lipoatrophy and Lipodystrophy

Primary lipoatrophy syndromes

Congenital generalized lipoatrophy (Fig. 3). This condition is also known as Seip-Berardinelli syndrome [23,24]. In this syndrome, children present with generalized absence of fat within the first year of life. This is followed by insulin resistance, acanthosis nigricans and diabetes mellitus before the teen-age years. Hypertriglyceridemia is severe and is accompanied by frequent bouts of pancreatitis. Affected patients have a high basal metabolic rate [25] and an increased appetite. Circulating leptin levels are usually quite low [26–28]. This syndrome has an autosomal recessive mode of inheritance, and has been described in all ethnic groups. We have observed a sexual dimorphism in the severity of metabolic complications. Female patients manifest diabetes and hypertriglyceridemia much earlier and usually more severely than the male siblings in the same family.

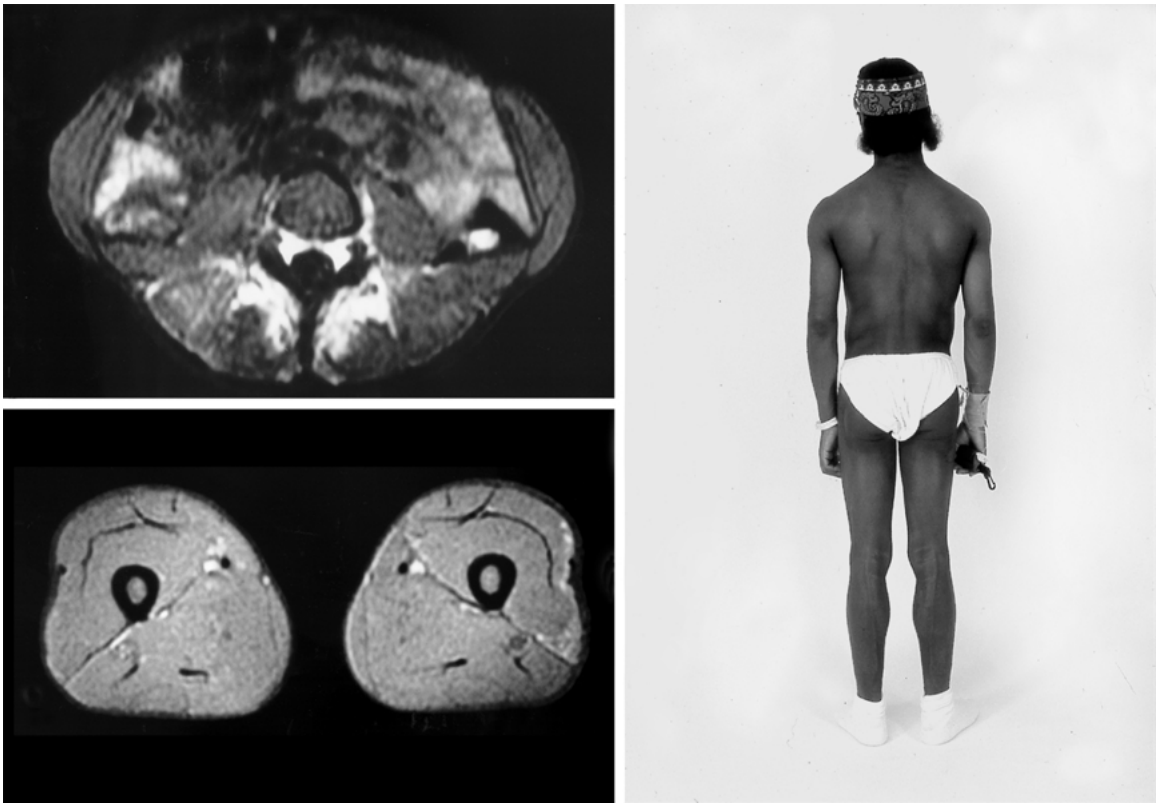

Fig. 3. *Congenital generalized lipoatrophy in a 16-year old girl. Picture (Right) and T1-weighted magnetic resonance images (Left). Transverse sections of the torso at the level of the fifth lumbar vertebra demonstrate markedly deficient subcutaneous and visceral fat (A). Transverse sections of the midthigh demonstrate absence of subcutaneous, deep, intrafascicular and marrow fat. Note again light-colored, lipid-filled muscle tissue (B). Note absence of fat throughout the body (C). Notice the differences between these images and those presented in Figures 1 and 2.*

Although well described clinically for decades, the molecular basis for congenital generalized lipoatrophy remained a mystery until quite recently. In the 1970s Foss et.al. demonstrated the presence of a urinary lipolytic factor in cases of congenital generalized lipoatropy; however, these studies have not been reproduced [29].

Initial work to identify the genetic cause of congenital generalized lipoatrophy started with candidate gene approach. The list of excluded genes was long, including genes encoding peroxisome-proliferator activated receptor-gamma, beta-3-adrenergic receptor, leptin, leptin receptor and lipoprotein lipase among others [30–32].

Progress to identify the disease genes came with positional cloning studies. The disease was initially mapped to chromosome 9q34 in some, but not all pedigrees [33]. Thus, it became evident that there were multiple causative genes. Magre et. al. cloned the first gene responsible from congenital generalized lipoatrophy using positional cloning and interval refining [34]. This gene is located on chromosome 11q13. This new gene was named Seipin as an attribute to Seip who is one of the first to describe the syndrome. The protein product of the Seipin gene is most likely a signaling molecule. It has three trans-membrane domains and the ligand is not known. The mouse orthologue of the gene is a G-protein related receptor gene [34]. Contrary to the predictions that prevailed prior to the discovery of this gene, Seipin is not abundantly expressed in the fat cells. It is expressed predominantly in the central nervous system and especially in the pituitary. Another location where it is expressed in high levels is the testes. This localization outside of adipose tissue implies a greater role for the central nervous system in energy storage and fuel metabolism than has currently been known and is likely to change our views on adipocyte differentiation mechanisms [34].

More recently, the second gene located on chromosome 9q34 was also cloned: 1-acylglycerol-3-phosphate O-acyltransferase 2 (*AGPAT2)* gene, AGPAT2 gene. AGPAT-2 is a 278 amino acid protein, belonging to the family of acyltransferases and catalyzes an essential reaction in the biosynthetic pathway of glycerophospholipids and triacylglycerol in eukaryotes, namely the conversion of lysophosphatidic acid to phosphaditic acid [35]. Congenital generalized lipodystrophy is the first documented human disease due to a genetic defect in this pathway. The exact cause of lipoatrophy is not clear, but we can formulate

some hypotheses. First, the aberrant AGPAT2 enzyme may cause lipodystrophy by resulting in "triglyceride-depleted adipocytes". However, it is important to note that engineered defects in rodents that interfere with triglyceride storage alone and result in "empty" adipocyte syndrome, do not lead to the metabolic consequences so long as the other functional capabilities (like endocrine function) of the adipocytes are not altered [36]. It is also likely that reduced AGPAT2 activity could increase tissue levels of lysophosphatidic acid, which may affect important adipocyte functions [37,38]. Lysophosphatidic acid is a ligand for G protein coupled receptors and may have a role in preadipocyte proliferation and adipogenesis [37–39]. Decreased AGPAT2 activity could also lead to reduced bioavailability of phosphatidic acid and phosphoglycerols (phosphatidylinositol, phosphatidylcholine and phosphatidylethanolamine), which are important in intracellular signaling and could affect adipocyte functions [40]. Future studies are needed to understand the exact mechanism of lipodystrophy seen with mutations in AGPAT-2. Another interesting question is whether overactivation of this enzyme can be a causative factor for human obesity.

There is also interest in identifying phenotypic differences between the patients harboring mutations on the different genes. First of all, there are some ethnic differences. So far, patients with Labenese descent have mutations exclusively on the Seipin gene and African American patients only have mutations on the AGPAT-2 gene. Mental retardation has been reported in some patients with Seipin mutations and not with AGPAT-2 mutations. Further work in this area may elucidate these differences and may shed some light on the biological function of these two genes.

There are still a few pedigrees with congenital generalized lipoatrophy who do not demonstrate mutations in either of these identified genes. Research is underway to identify other gene(s) responsible from congenital generalized lipoatrophy. Rajab et al. reported observations on 17 patients with congenital generalized lipodystrophy in Oman which suggested the existence of a rare form of the disorder [41]. All children had widespread absence of adipose tissue from infancy together with apparent muscle hypertrophy and hepatomegaly. The patients did not appear to represent a single homogeneous entity, and could be subclassified into 2 distinct groups. In the first group of 7 cases, the features were similar to other published cases with acanthosis nigricans, raised insulin levels, and insulin resistance. In this group there was an association between the degree of acanthosis nigricans and the severity of the disorder. Molecular analysis of these cases showed homozygosity for a mutation at the Berardinelli Seip Congenital Lipodystrophy 2 *(BSCL2)* locus on 11q13 in 4 of the 7 cases. In the second group of 10 cases, there were striking abnormalities in both skeletal and nonskeletal muscle, including reduced exercise tolerance, and percussion myoedema. None of these children had insulin resistance or early endocrine abnormalities. All 10 had hypertrophic pyloric stenosis operated on in the first 6 weeks of life. The veins were very prominent (phlebomegaly) in the skin and cutis marmorata was present. Cardiac abnormalities with cardiac hypertrophy and arrhythmias were features later in childhood. There was a history of sudden death in some of the sibs. There was evidence against homozygosity in some cases for the known loci of BSCL, and Rajab et. al. suggested that this group may represent a new clinical syndrome with lipodystrophy at a different locus [41].

Familial partial lipodystrophy (FPLD, Dunnigan's syndrome) (Fig. 4). Also referred as Kobberling-Dunnigan syndrome, this condition is inherited in an autosomal dominant fashion. It has been seen mostly in Caucasians of Northern European descent, but pedigrees of Asian descent have also been described. It is usually impossible to distinguish affected patients from unaffected ones before the onset of puberty. Patients are born with normal fat distribution but notice loss of subcutaneous fat in the extremities and trunk with early puberty. This is followed by increased fat in the face and neck as puberty is completed [42,43]. The visceral fat and interfascicular intramuscular fat depots are preserved [44,45]. While the disease affects both sexes, the phenotype is much easier to discern in females leading to ascertainment bias of female probands. Overall, female patients develop diabetes and dyslipidemia earlier and more severely. For example, from our case series, affected females develop diabetes about 73% of the time and hypertriglyceridemia 90% of the time. In contrast, these incidences are 36% and 45% respectively, in affected male individuals. Our observations are similar to published observations of another group [46].

An exciting advance in the understanding of the syndrome has been the discovery that the disease is caused by mutations in the lamin A/C gene (LMNA) located at 1q21–23 [47–51]. Lamin A and C are alternatively spliced products of the same gene and are ubiquitously, but not equally expressed [52]. They belong to a family of intermediate filament proteins that form the nuclear matrix [53,54], which is located just inside the nuclear membrane. Lamins dimerize and oligomerize within the structure of the nuclear matrix [54]. There is developmental regulation of the expression of lamins in humans.

Besides Dunnigan's FPLD, multiple other diseases are associated with mutations in LMNA: Emery Dreyfus muscular dystrophy (a progressive muscular dystrophy of upper and lower extremity muscles with prominent contractures of ankles and elbows, and cardiac conduction

abnormalities) [55,56], hereditary limb-girdle muscular dystrophy [57], a familial cardiomyopathy associated with conduction abnormalities [58,59], hereditary Charcot-Marie Tooth Neuropathy type 2 [60] and finally another complex syndrome with partial lipodystrophy mandibuloacral dysplasia [61]. The degree of overlap between these diseases and FPLD is subject of research. In addition, how the mutations in the LMNA result in multiple different diseases and how the mutations in a ubiquitously expressed gene cause various syndromes with a strong regional distribution are questions still awaiting answers. As far as FPLD is concerned, investigation of expression patterns of various lamins in different adipose depots (visceral versus subcutaneous) did not provide any clues into the mechanism of disease of FPLD [62]. Likewise, investigation of the nuclear targeting or interaction with dimerization partner emerin in a common mutant form seen in FPLD did not elucidate any abnormalities [63].

Partial lipodystrophy associated with dominant negative mutations on PPAR-gamma gene (late-onset familial partial lipodystrophy). Barroso and colleagues described two probands with severe insulin resistance and hypertension as well as severe acanthosis nigricans [64]. Initially, no changes in body composition were reported. However, careful body composition studies revealed that these patients have significant fat loss in the lower extremities, particularly in the buttock region. The onset of fat loss is not at birth, but develops sometime in adulthood. There is also increased visceral adiposity. Agarwal and Garg described another female patient with a different mutation on PPAR-γ gene who had a similar body fat distribution without any hypertension and acanthosis nigricans [65]. These observations suggest that dominant-negative mutations of the PPAR-γ gene result in both severe insulin resistance and also an abnormality in body fat distribution that manifests later in life.

Congenital syndrome complexes associated with lipoatrophy

There are also other complex monogeneic syndromes that are not characterized as primary lipodystrophy syndromes but are associated with abnormal body fat distribution among other complex abnormalities. Progeria syndromes such as Werner's (adult progeria syndrome, Figure 5(a), [66] and Cockayne's Syndrome (one of the juvenile progeria syndromes) [67,68], carbohydrate-deficient glycoprotein syndrome Type 1 [69], SHORT syndrome (an acronym for short stature, hyperextensibility, hernia, ocular depression, Rieger anomaly and teething delay) [70,71] and mandibuloacral dysplasia (Fig. 4(b)) [72,73] are among such syndromes. AREDYLD syndrome (acral, renal and ectodermal dysplasia in association with generalized lipodystrophy) [74] probably represents another complex progeria syndrome.

Mandibuloacral dysplasia (MAD, Figure 5(b)) is a genetic disorder with multi-system involvement and autosomal recessive inheritance. This extremely rare syndrome is characterized by multiple skeletal abnormalities, acroosteolysis, joint and skin problems and is also associated with lipodystrophy and metabolic abnormalities [72,73]. In this condition, the predominant fat loss is from the extremities and trunk with increased visceral adiposity [75]. Recently Novelli et al. analyzed five consanguineous Italian families and demonstrated linkage of MAD to chromosome 1q21, by use of homozygosity mapping. They then sequenced the LMNA gene and identified a homozygous missense mutation (R527H) that was shared by all affected patients [61]. Patient skin fibroblasts showed nuclei that presented abnormal lamin A/C distribution and a dysmorphic envelope, thus demonstrating the pathogenic effect of the R527H LMNA mutation [61].

Some unusual congenital associations such as Vitamin D resistance and persistent Mullerian ducts [76], retinal pigmentation abnormalities [77] and sensorineural deafness [78] have been reported in association with lipoatrophy in isolated cases. These unusual patients present as pediatric patients or young adults.

In our case series, we have encountered an autosomal dominant form of congenital lipodystrophy (characterized by absence of fat from face, upper trunk, arms and below the knees) associated with a progressive neurodegenerative disorder (characterized by progressive spinocerebellar ataxia, pyramidal weakness and spasticity, and autonomic insufficiency) and congenital cataracts. In this small pedigree, affected individuals also have insulin resistance and dyslipidemia and both the neurodegenerative disorder and dyslipidemia are more severe in affected female members [79].

Acquired Syndromes of Lipoatrophy

Syndromes of acquired generalized lipoatrophy are hard to categorize due to the apparent heterogeneity of case reports. As it is clear from the genetic syndromes, certain genetic defects do not manifest an abnormality until a certain point in life. Hence some genetic syndromes can present as so-called "acquired" syndromes. Especially, in the case of recessive disorders, the proband may be the only affected patient and it may be difficult to tease out a genetic pattern of inheritence. Though there are two eponyms used in the literature to describe acquired generalized and acquired partial lipodystrophy syndromes, we will use the descriptive names rather than the eponyms for these syndromes until better molecular tools enable us to categorize these syndromes precisely.

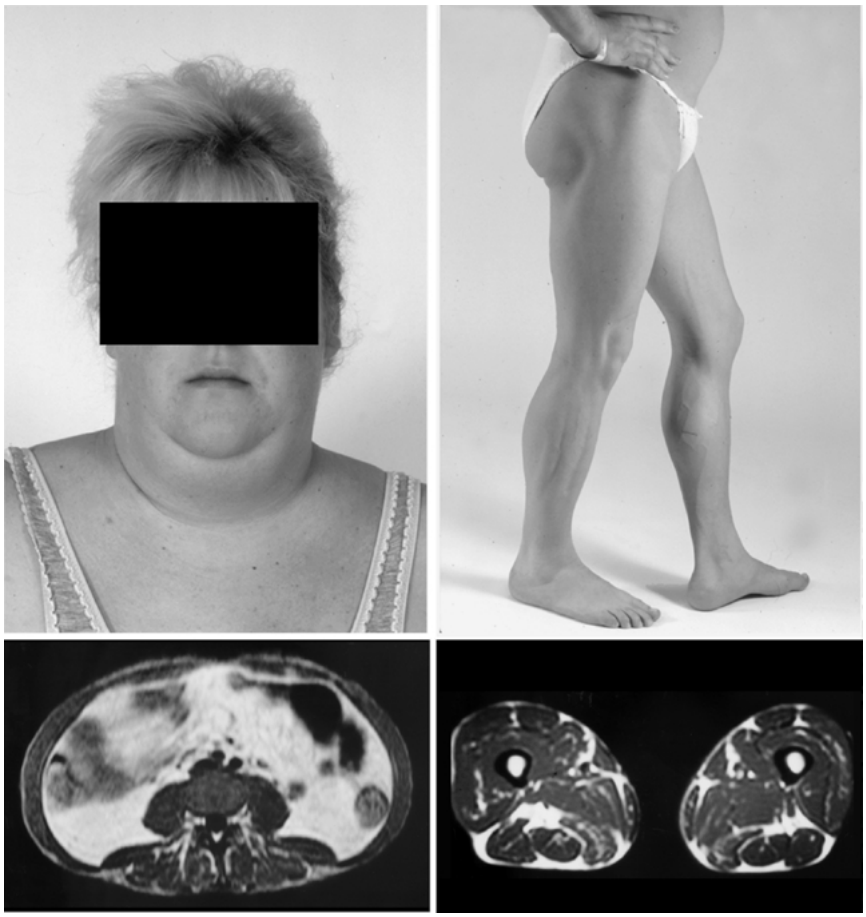

Fig. 4. *Dunnigan's familial partial lipodystrophy. (Top) Pictures of a 26-year old female. Note increased fat around the face/neck (A) and deficiency in the gluteal region and lower extremities (B). (Bottom) T1-weighted magnetic resonance images. Transverse sections of the torso at the level of the fifth lumbar vertebra demonstrate markedly deficient subcutaneous and increased visceral fat (C). Transverse sections of the midthigh demonstrate absence of subcutaneous fat with preservation of deep, intrafascicular and marrow fat (D).*

Acquired generalized lipoatrophy

Lawrence described acquired generalized lipoatrophy with the onset of the disease during childhood [80]. His original report remains an excellent description of generalized lipoatrophy. Fat loss is usually a remarkable event leading to a dramatic change in physical features (Fig. 6). The median time to develop diabetes after loss of fat tissue is about 4 years. Both basal metabolic rate and hepatic glucose output are increased. While it is known that these patients lack fully differentiated adipocytes, it is not clear whether they also lack adipocyte precursors [81]. Patients with this type of lipodystrophy may have very severe fat loss, including retroorbital fat and supportive fat in their hands, feet and genital area. Bone marrow fat is lost in some cases, while preserved in others.

Acquired partial lipodystrophy

The case reports that refer to Barraquer-Simons syndrome describe a wide-range of variation with few shared features. Patients usually are women in their second or third decades, who also have a well described autoimmune disorder such as scleroderma or glomerulonephritis, presenting with partial fat loss, [15,82,83]. Fat loss usually starts from the face and descends downward until the gluteal line. There is usually increased adiposity in unaffected fat depots (lower extremities). The prevalence of diabetes and hypertriglyceridemia is about 50% in these cases and seems to coseggragate with lower total body fat in our series.

Other associated conditions

Some cases of acquired lipodystrophy occur in the presence of a population of circulating autoantibodies or an association with another autoimmune disease (e.g. juvenile dermatomyositis) and therefore are thought to be autoimmune in nature. There is a clear association of lipodystrophy with juvenile dermatomyositis [84–87]. These patients typically present before teen-age years. The fat loss can be both generalized or partial. There is usually increased visceral fat despite very severe preipheral fat loss

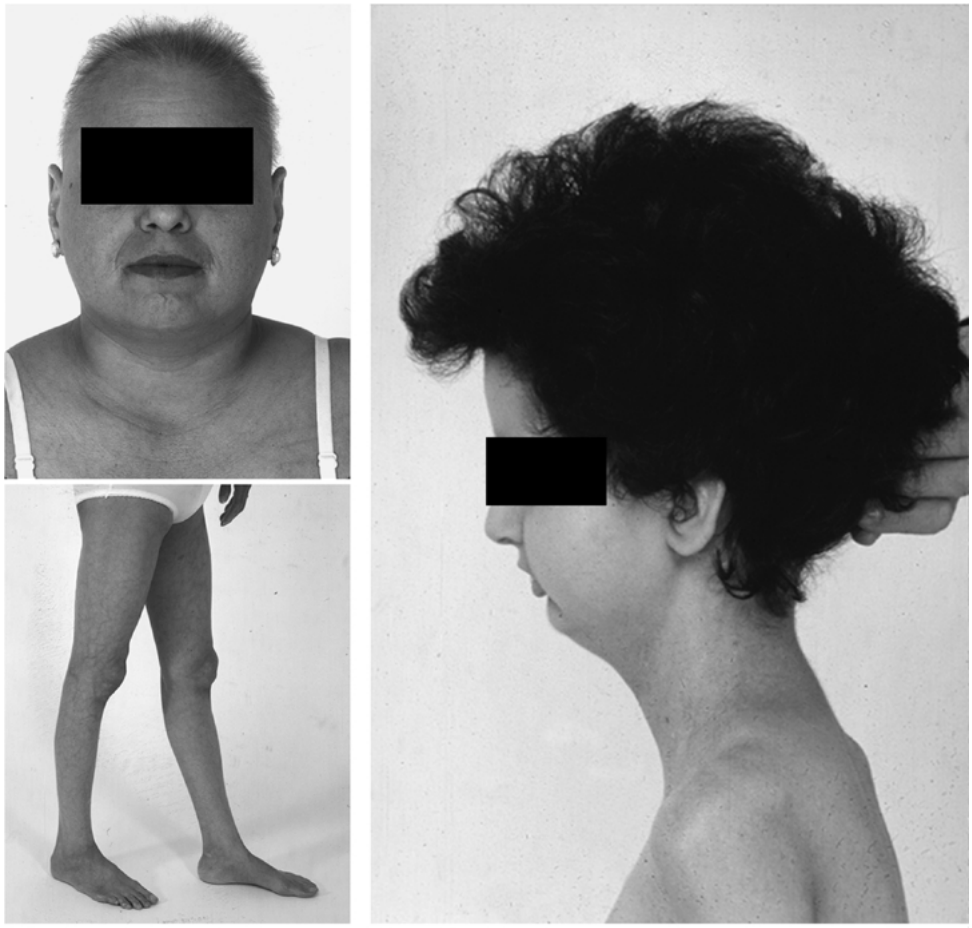

Fig. 5. *(A) Werner's Syndrome in a 37-year old woman. Clinical features evident include premature aging, allopecia, scleroderma-like changes in the skin and peripheral lipoatrophy as shown. Insulin-resistant diabetes is an associated feature. (B) Mandibuloacral dysplasia in a 14 year old girl. This rare recessive syndrome is characterized by acroosteolysis, widened sutures, hypoplastic mandible (shown) and clavicles (shown). Marked peripheral lipoatrophy and insulin resistance are associated features.*

and a specific asymmetric pattern of fat loss on extremities (Fig. 7).

Panniculitis, a chronic (as defined by lasting 3 months or longer), generalized inflammation of the subcutaneous tissue, has been observed either clinically or proven by biopsy to proceed the loss of fat in some cases of lipodystrophy [88]. The evidence for long-sought specific anti-fat cell autoantibodies or specific activated T-cell clones is still weak

A portion of acquired lipodystrophy patients are demonstrated to have low C3 levels [89] and it was speculated that adipsin, a factor produced by fat cells was responsible for the loss of fat due to alternative activation of complement pathway. Generalized or partial fat loss has been described in association with familial [90] or acquired hypocomplementemia [91–93].

Some patients infected with HIV while being aggressively treated with protease inhibitors, develop a partial lipoatrophy. The characteristic loss of subcutaneous fat occurs in the face, extremities and trunk. In contrast, visceral fat increases and a "buffalo hump" like that is seen in Cushing syndrome develops [94–96]. The lipodystrophy is accompanied by the development of insulin resistance and hypertriglyceridemia. The changes in body composition and metabolic parameters are usually apparent within 3 to 6 months of therapy. There is a quicker onset of this partial lipoatrophy when more than one protease inhibitor is used. The syndrome is recognized in both sexes and in pediatric as well as adult patients. Why do treated HIV patients develop this characteristic phenotype? One hypothesis is that an aspartyl protease (like the HIV protease) may be important in the differentiation of adipocytes. In support of this hypothesis, several groups reported that protease inhibitors blocked preadipocyte differentiation in vitro [97,98]. Interestingly, some groups have reported the development of a similar phenotype when HIV-infected patients are treated aggressively with other antiretroviral agents other than protease inhibitors

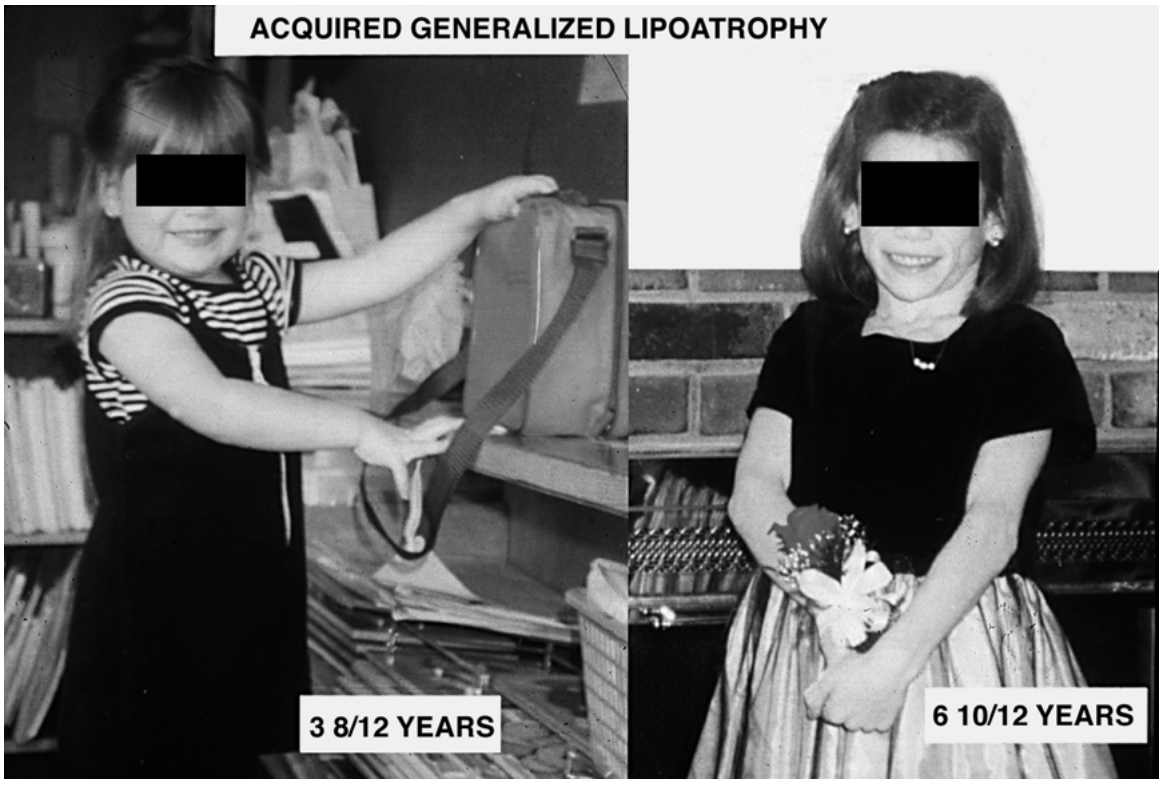

Fig. 6. *Acquired generalized lipoatrophy. The patient had completely normal fat distribution at age 3 8/12 years old (left) and acutely lost her body fat with a febrile illness at age around age 6 (shown on the right).*

(including nucleoside analogues) [99–101]. This suggests that the lipodystophy may be related to aggressively treated HIV infection rather than to a specific therapy [99,102]. Further investigations are underway to better categorize the fat tissue changes and metabolic consequences during HIV therapy. While the HIV related lipodsytrophy is the most prevalent form of lipodystrophy, the details of this unique syndrome is not in the scope of this review.

Clinical Abnormalities Observed in Lipoatrophy/Lipodystrophy Syndromes: A Recapitulation of Shared Features (Table 2)

Different syndromes of lipodystrophy have a heterogeneous clinical presentation; however, findings of insulin-resistance and hypertriglyceridemia are seen in all forms of lipoatrophy. A greater loss of adipose tissue is associated with an increased severity of the metabolic abnormalities. The insulin resistance leads to hyperinsulinemia, and the associated clinical features of acanthosis nigricans and hyperandrogenism in female patients.

The reproductive abnormalities are more complicated than simple hyperandrogenism and polycystic ovaries in the patients with more severe forms of lipoatrophy. About 50% of all the patients with generalized lipoatrophy and the majority of the female patients (85%) present with very low LH levels, more consistent with hypogonadotropic hypogonadism. This creates a paradox with the findings on ovarian imaging studies since these usually reveal enlarged, polycystic ovaries. Hence, it appears that severe hyperinsulinemia in the most severe cases of lipoatrophy is sufficient to drive the ovarian enlargement and associated hyperandrogenism without any apparent stimulation from the pituitary [103].

Patients with early-onset hyperinsulinemia (as in congenital generalized lipoatrophy) develop acromegaloid features with soft tissue hyperplasia, somatomegaly and bony abnormalities [104]. Cardiomyopathy is also described in some of these cases [105,106].

Another notable finding in the most severely fat deficient patients is their food-seeking behavior. They may consume large amounts of food (similar to patients with bulimia) and get the urge to eat frequently. This behavior is associated with low levels of circulating leptin which may contribute to the increased appetite [28].

Diabetes will develop in the setting of long-standing hyperinsulinemia due to beta-cell failure. Diabetic retinopathy, nephropathy, neuropathy, gastroparesis as well as coronary heart disease are seen in these patients with uncontrolled and longstanding hyperglycemia.

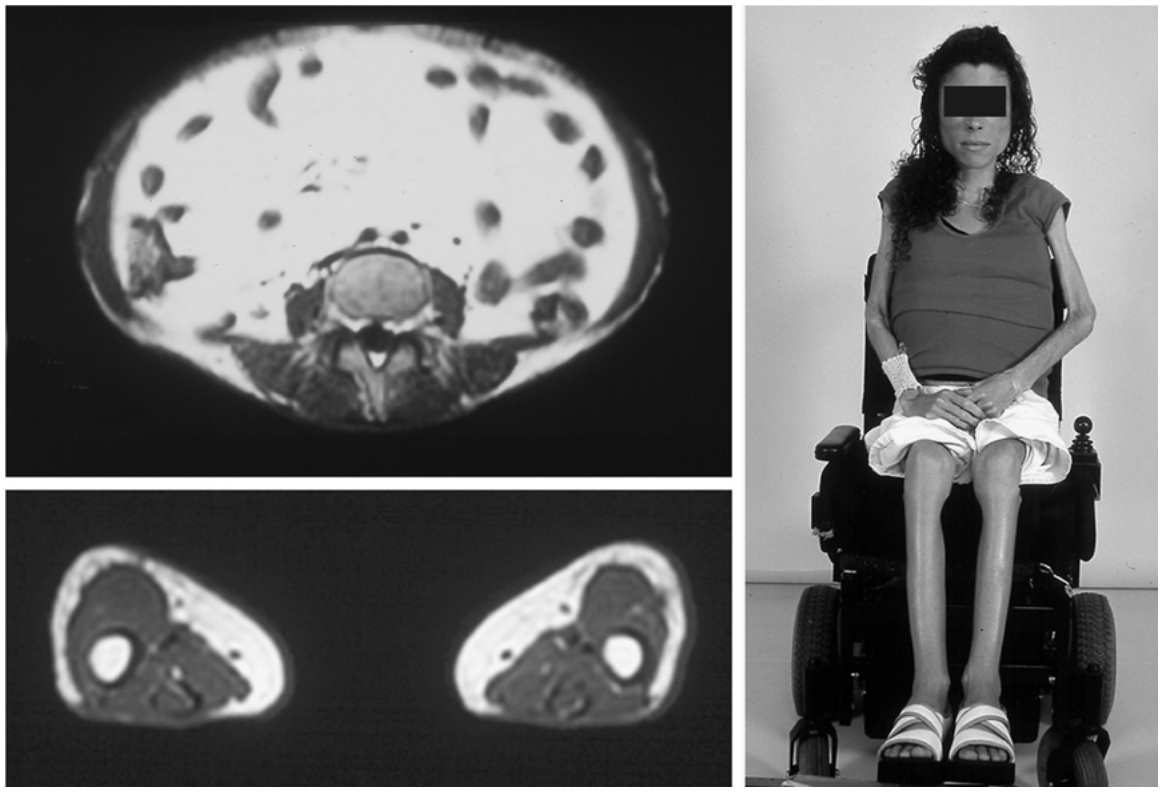

Fig. 7. A case with severe juvenile dermatomyositis and generalized lipodystrophy. The physical appearance of the 19-year old patient is presented (right). She has severe loss of both muscle and fat tissue. T1-weighted magnetic resonance images of the patient are also presented (left). Transverse sections of the torso at the level of the fifth lumbar vertebra demonstrate markedly deficient subcutaneous and markedly increased visceral fat (top). Transverse sections of the midthigh demonstrate asymmetrical absence of subcutaneous fat with preservation of medial subcutaneous fat and marrow fat (bottom).

There is a high incidence of proteinuria leading to chronic renal failure among patients with lipoatrophy syndromes. While diabetic nephropathy seem to play a role in some of these patients, it does not account for all the cases [107]. The patients with hypocomplementemia develop membranous glomerulonephritis [108]. Focal segmental glomerulosclerosis and tubular lipidosis are also among various kidney pathology that have been described in association with lipoatrophy [109].

Patients with lipoatrophy have a dyslipidemia that is primarily characterized by elevated triglycerides. This is thought to be secondary to decreased storage site for triglycerides. There is also strong evidence from animal models that lipid synthesis is paradoxically increased in the liver possibly due to decreased signal coming from the adipocyte that "sufficient" lipid storage is achieved. Leptin may be this crucial signal since this abnormality gets corrected in one animal model of lipoatrophy upon leptin replacement [110].

Most patients have a low HDL and some may have a high LDL. Particularly, the patients with one type of partial lipodystrophy, namely familial partial lipodystrophy of the Dunnigan type have elevated LDL and a markedly increased risk of coronary artery disease [111].

It is thought that due to a relative paucity of adipose tissue, there is excessive accumulation of triglycerides in multiple locations, most notably in the liver and to some extent in the muscle [112]. Increased deposition of fatty acids and triglycerides in the muscle or in the beta-cell may be responsible for causing insulin resistance (lipotoxicity) [113–115]. It is possible that the accumulation of triglycerides in hepatocytes causes the injury associated with non-alcoholic steatohepatitis (NASH) [116]. In patients will all types of lipoatrophy there is an increased incidence of non-alcoholic steatohepatitis (NASH) compared to both the diabetic and general population. This condition is seen in at least a third of patients with lipoatrophy and may progress into end-stage liver failure.

We have previously observed that the respiratory quotient (RQ) is elevated in patients with lipoatrophy/lipodystrophy [117]. The RQ is the ratio of carbon dioxide production to oxygen consumption and reflects the relative contributions of carbohydrates and fat in providing fuel for metabolism. The elevated RQ suggests that there is an increase in fuel consumption relative to synthesis.

Table 1. *Genetic syndromes of lipoatrophy*

Syndrome	Lipoatrophy	Gene/Locus	Inheritence	OMIM[a]
Primary lipoatrophy syndromes				
CGL[b]	Generalized	9q34	AR[c]	269700
(Seip-Berardinelli)	See text for details[d]	AGPAT-2		
		11q13		
		Seipin gene		
		Putative CGL-3		
Dunnigan syndrome	Familial partial	1q21-22	AD[e]	151660
	See text for details	Lamin A/C		
Late-onset FPLD	Familial partial	3p25	AD	604367
	See text for details	PPAR-γ		
Others	Numerous distributions	Unknown	AD/AR	N/A
Complex syndromes associated with lipoatrophy				
Mandibuloacral dysplasia	Congenital, partial	1q21-22	AR	248370
	Involves extremities	Lamin A/C		
Werner syndrome	Congenital, partial	8p12	AR	277700
	Involves extremities	Werner's Helicase		
Cockayne syndrome	Congenital, partial	5	AR	216400
	Involves extremities	CSA		
Carbohydrate-deficient	Transient, partial	16p.13.3	AR	212065
Glycoprotein syndrome	Buttocks	PMM1 and 2[f]		
SHORT[g] syndrome	Generalized, congenital	Unknown	AR	269880
AREDYLD[h] syndrome	Generalized, congenital	Unknown	Unknown	207780

[a]Online-Mendelian Inhertance of Man, reference 132, data base providing information about genetic syndromes.
[b]Congenital generalized lipoatrophy.
[c]Autosomal recessive.
[d]Evidence for genetic heterogeneity.
[e]Autosomal dominant.
[f]Phosphomannomutase 1 and 2.
[g]Short stature, hyperextensibility, hernia, ocular depression, Rieger anomaly, and teething delay.
[h]Acrorenal field defect, ectodermal dysplasia, and lipoatrophic diabetes, not clear if this is a variation of Berardinelli-Seip syndrome.

Therefore, either the rate of fatty acid oxidation is decreased or the rate of lipogenesis is increased. Either change might contribute to the observed elevation in the levels of free fatty acids and triglycerides [118]. Furthermore, because fatty acids are known to antagonize insulin's effects upon glucose metabolism, this provides another mechanism to account for the state of insulin resistance [119].

Treatment of Lipoatrophy/Lipodystrophy

The clinical problems requiring treatment in lipoatrophy syndromes are diabetes, hypertriglyceridemia and cosmetic problems. The cosmetic problems are quite severe especially for the female patients and can be emotionally scarring. It is important not to underestimate the cosmetic issues while taking care of the metabolic problems. In patients with lower bady fat abundance and upper body fat loss, local fat implantation taken from the area of excess and implanted to the face have produced satisfying results. Facial silicon implants in a few patients with HIV-lipodystrophy have also produced successful cosmetic recovery. It is important to understand patients' expectations and wishes and referral to a plastic surgery center with academic interest in the syndromes may be valuable.

Treatment of diabetes in lipoatrophy

Although there are several classes of anti-diabetic drugs marketed in the U.S., it is difficult to achieve good glycemic control (glycated hemoglobin $<7.2\%$) in most of the patients with lipoatrophic diabetes. There are five groups of pharmaceuticals available to treat diabetic patients [120] all of which may be used to treat lipoatrophic patients: insulin secretagogues, biguanides (metformin), thiazoladienediones (pioglitazone, rosiglitazone), intestinal enzyme inhibitors (acarbose), and insulin itself.

Insulin. Because of their severe insulin resistance, it is frequently necessary to administer extremely high doses (e.g., in excess of 1000 units per day) in patients with various syndromes of lipoatrophy [121]. The volume of injections are more difficult to tolerate in younger patients. Nevertheless, insulin remains the only approved medication for treatment of children with diabetes.

Table 2. *Characteristics of patients with lipoatrophy*

Clinical characteristics:

- Fat loss
- Acanthosis nigricans
- Hyperandrogenism in females
- Primary amenorrhea in females
- Muscular hypertrophy
- Cardiomyopathy in some patients
- Hepatomegaly or cirrhosis
- Voracious appetite
- Increased sweating and heat intolerance

Laboratory characteristics

- Hyperinsulinemia
- Hyperglycemia
- Hypertriglyceridemia
- Abnormal cholesterol profile (low HDL, sometimes high LDL)
- Elevated free fatty acids
- Low leptin levels and other adipocyte hormones such as adiponectin
- Elevated liver function tests
- Increased glomerular filtration rate
- Proteinuria sometimes in the nephrotic range
- Increased RMR
- Increased respiratory quotient

Radiological characteristics:

- Low body fat by DEXA
- Absent or increased fat compartments on T1 weighted MRI imaging depending on the syndrome
- Normal bone mineral density by DEXA
- Lytic lesions on long bones and osteosclerosis
- Increased liver and muscle triglyceride content by NMR spectroscopy
- Hepatic steatosis by ultrasound

Tissue chararecteristics:

- Fat tissue: Absent fat depots
- Muscle: Increased intramyocellular lipids, muscular hypertrophy, myoedema
- Liver: Non-alcoholic steatohepatitis and/or cirrhosis in the liver
- Kidney: Diabetic nephropathy, membranous glomerulonephritis, tubular lipidosis, focal segmental glomerulosclerosis
- Islet cells: Hyperplasia, increased lipid droplets, amyloidosis
- Bone marrow: Fat absent in congenital generalized lipoatrophy

Insulin secretagogues. The principal mechanism of action for this class of drugs is to promote insulin secretion by beta cells [122]. Because patients with isolated insulin resistance may not have an independent defect in insulin secretion, sulfonylureas are frequently ineffective in patients with lipoatrophic diabetes.

Metformin. This drug works primarily through inhibiting heptic glucose output. We (and others) have observed that it may help to decrease insulin requirements in some patients with lipoatrophy/ lipodystrophy. To our knowledge, there are no systematic trials looking at the efficacy of this drug in lipoatrophy/lipodystrophy. While the pediatric experience with metformin is growing, it was only recently approved by the U.S Food and Drug Administration to be used in children over the age of 10. Therefore, it needs to be administered by clinicians who have prior experience with treatment with this drug, ideally in centers specialized in treating children with unusual forms of diabetes.

Acarbose. This drug interferes with GI absorption of many carbohydrates [123]. While we are not aware of systematic studies of the efficacy of this drug in patients with lipoatrophy, it has relatively limited efficacy to decrease glucose levels in type 2 diabetes mellitus.

Thiazolidinediones. This class is the newest addition to oral hypoglycemic agents. Members of this class are agonists of peroxisome-proliferator activated receptor-gamma (PPAR-gamma); thereby, stimulating adipocyte differentiation [124]. *In vivo*, this class of drugs functions as insulin-sensitizers and increase insulin-stimulated glucose uptake by the muscle [125,126]. Troglitazone was the first member to be approved by the US Food and Drug Administration. These effects of thiazolidinedione compounds seemed ideally suited to treat the problems encountered in lipoatrophy/lipodystrophy syndromes. In addition, troglitazone exerted favorable effects in an animal model of lipoatrophy [127]. We thus undertook a treatment trial in these patients with troglitazone [117]. The primary end-points were metabolic control and adipose tissue mass. Six months of troglitazone therapy led to significant improvement in metabolic control with a reduction in HbA1c, triglycerides, and free fatty acids [117]. In addition, there was a small, but statistically significant increase in body fat [117]. Interestingly, the increase was predominantly in the subcutaneous compartment. Furthermore, body weight did not change significantly and there was a decrease in liver size [117]. Despite the favorable effects of troglitazone, the FDA withdrew troglitazone from the US market in March 2000 due to concerns over hepatotoxicity. The newer members of the class, rosiglitazone and pioglitazone, remain in clinical use. The preclinical studies with these two medications suggested that they did not have the same risk of hepatotoxicity. Since the use of thiazolidinediones require judicious monitoring for side-effects, their use should be supervised by clinicians who are experienced in administering these medications after careful assessment of risk: benefit ratio.

Treatment of dyslipidemia in lipoatrophy

The dyslipidemia of severe lipoatrophy is difficult to treat with the currently available therapeutic interventions

which still results in significant morbidity and mortality from this condition. Patients with triglyceride levels over 1000 mg/dl are at risk of developing acute pancreatitis. Recurrent episodes lead to pancreatic insufficiency. Chronically elevated triglycerides in the setting of hyperinsulinemia and low HDL increase the predisposition for coronary artery disease. Severely elevated triglycerides may lead to eruptive painful cutaneous xanthomata [128].

Troglitazone was remarkable in its ability to improve hypertriglyceridemia in addition to improving glycemia. As niacin is known to worsen glycemic control, we prefer to use fibrates and statins in these severely insulin resistant lipoatrophic patients. Both fibrates and statins may need to be used in combination with careful monitoring for side-effects. Again, the pediatric experience with these medications are extremely limited.

Limitation of caloric intake may be useful for short-term results, but is not possible to implement for long-term management as dietary fat is required for proper growth and development. Medium chain triglycerides and fish oil have not been tested in a systematic fashion, but may prove to be useful. We have attempted to use intestinal lipase inhibitors in a few of the most severely affected pediatric patients with some positive results. Finally, we have employed long-term plasmapheresis in one patient with extreme hypertriglyceridemia with moderate clinical success [128].

Leptin replacement therapy: From the laboratory to clinical trials

As mentioned earlier, the metabolic abnormalities of diabetes and hypertriglyceridemia in lipoatrophy may be caused by the absence of hormones produced by fat cells. Shimomura et al. administered one such hormone, leptin, to lipoatrophic mice. Prior to therapy, these mice exhibited diabetes, hypertriglyceridemia, hepatic steatosis and severe leptin deficiency. Interestingly, 3 weeks of leptin therapy ameliorated all the metabolic abnormalities and also decreased the degree of steatosis in the liver [129]. These results from animal models warranted a clinical trial which was recently published.

In the published portion of the trial [28], 9 female patients with various forms of lipodystrophy (5 with congenital generalized, 3 with acquired generalized and 1 with Dunnigan's familial partial lipodystrophy) were treated with 4 months of subcutaneous leptin administered to achieve physiological concentrations of leptin. Leptin levels increased from a mean of <2 ng/mL to a mean of 12 ng/mL, indicating that that the goal of leptin replacement was largely achieved. There was a remarkable decrease in both hyperglycemia and hypertriglyceridemia as well as improved total body insulin sensitivity and decreased liver volumes (Table 3). In addition, the reproductive abnormalities were studied in 7 of these patients. Leptin therapy corrected the amenorrhea seen in 5 of the 5 patients with intact reproductive systems and normalized the attenuated LH response to LHRH stimulation [103].

Table 3. *Efficacy of leptin in the treatment of lipodystrophy [28]* ($n = 9$) *[28]*

Parameter	Baseline	4-Months of therapy	P-value
HbA1c (%)	9.1	7.2	<0.001
Triglycerides (mg/dL)	1405	348	<0.001
Free fatty acids (mcmole/L)	1540	790	<0.05
K-constant @ insulin tolerance test	0.0071	0.0169	<0.04
Liver volume (cc.s)	3097	1998	<0.002

This leptin-replacement study is likely to inspire similar studies using replacement of adipocyte-specific hormones to treat metabolic abnormalities. Leptin therapy corrects metabolic abnormalities to a great extent in the majority of the patients. However, leptin is certainly not the only hormone made by adipocytes. In fact, in one animal model of lipoatrophy, combined replacement of both leptin and adiponectin result in better metabolic control compared to leptin alone [130]. Haque et al. recently reported that patients with most severe forms of lipodystrophy are deficient in adiponectin levels in addition to leptin [131]. Hence, combined replacement appears as a rational approach when recombinant adiponectin is available for human studies.

Conclusions

Human lipodystrophy syndromes encompass a heterogenous spectrum of disorders characterized by loss of body fat and associated with severe insulin resistance and hypertriglyceridemia. Studies undertaken to search the molecular etiologies of these syndromes have uncovered three completely unexpected genes. Currently researchers are trying to place these genes on known paradigms of adipocyte differentiation. All these gene products are also potential targets for developing novel therapies against the 21st century epidemic, obesity. On the other hand, pathophysiological and therapeutic studies carried out in patients with these disorders and in animal models have taught important lessons about the importance of fat tissue in maintaining normal insulin sensitivity. It is now clear that the adipocyte is an endocrine organ, playing a critical role in glucose and lipid metabolism.

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References

1. Foster DW. The lipodystrophies and other rare disorders of the adipose tissue. In: Fauci AS et al., eds. *Harrison's Principals of Internal Medicine*. New York: McGraw-Hill, 1998:2209–2214.
2. Yura S, Ogawa Y, Sagawa N, Masuzaki H, Itoh H, Ebihara K, Aizawe-Abe M, Fujii S, Nakao K. Accelerated puberty and late-onset hypothalamic hypogonadism in female transgenic skinny mice overexpressing leptin. *J Clin Invest* 2000;105:749–755.
3. Aizawa-Abe M, Ogawa Y, Masuzaki H, Ebihara K, Satoh N, Iwai H, Matsuoka N, Hayashi T, Hosoda K, Inou G, Yoshimasa Y, Nakao K. Pathophysiological role of leptin in obesity-related hypertension. *J Clin Invest* 2000;105:1243–1252.
4. Waller EG, Wade AJ, Treasure J, Ward A, Leonard T, Powell-Tuck J. Physical measures of recovery from anorexia nervosa during hospitalised re-feeding. *Eur J Clin Nutr* 1996;50:165–170.
5. Horska A. Use of magnetic resonance in body composition studies: Applications to research on caloric restriction and exercise. *Coll Antropol* 1998;22:385–392.
6. Wu Z, Rosen ED, Brun R, Hauser S, Adelmant G, Troy AE, McKeon C, Darlington GJ, Spiegelman BM. Cross-regulation of C/EBP alpha and PPAR gamma controls the transcriptional pathway of adipogenesis and insulin sensitivity. *Mol Cell* 1999;3:151–158.
7. Kim JB, Wright HM, Wright M, Spiegelman BM. ADD1/SREBP1 activates PPARgamma through the production of endogenous ligand. *Proc Natl Acad Sci USA* 1998;95:4333–4337.
8. Kim JB, Sarraf P, Wright M, Yao KM, Mueller E, Solanes G, Lowell BB, Spiegelman BM. Nutritional and insulin regulation of fatty acid synthetase and leptin gene expression through ADD1/SREBP1. *J Clin Invest* 1998;101:1–9.
9. Peterfy M, Phan J, Xu P, Reue K. Lipodystrophy in the fld mouse results from mutation of a new gene encoding a nuclear protein, lipin. *Nat Genet* 2001;27:121–124.
10. Reitman ML, Arioglu E, Gavrilova O, Taylor SI. Lipoatrophy revisited. *Trends Endocrinol Metab* 2000;11:410–416.
11. Gavrilova O, Marcus-Samuels B, Graham D, Kim JK, Shulman GI, Castle AL, Vinson C, Eckhaus M, Reitman ML. Surgical implantation of adipose tissue reverses diabetes in lipoatrophic mice. *J Clin Invest* 2000;105:271–278.
12. Fruebis J, Tsao TS, Javorschi S, Ebbets-Reed D, Erickson MR, Yen FT, Bihain BE, Lodish HF. Proteolytic cleavage product of 30-kDa adipocyte complement-related protein increases fatty acid oxidation in muscle and causes weight loss in mice. *Proc Natl Acad Sci USA* 2001;98:2005–2010.
13. Hu E, Liang P, Spiegelman BM. AdipoQ is a novel adipose-specific gene dysregulated in obesity. *J Biol Chem* 1996;271:10697–10703.
14. Matsuzawa Y, Funahashi T, Nakamura T. Molecular mechanism of metabolic syndrome X: Contribution of adipocytokines adipocyte-derived bioactive substances. *Ann N Y Acad Sci* 1999;892:146–154.
15. Taylor SI, Arioglu E. Syndromes associated with insulin resistance and acanthosis nigricans. *J Basic Clin Physiol Pharmacol* 1998;9:419–439.
16. Kayikcioglu A, Akyurek M, Erk Y. Semicircular lipoatrophy after intragluteal injection of benzathine penicillin. *J Pediatr* 1996;129:166–167.
17. Reeves WG, Allen BR, Tattersall RB. Insulin-induced lipoatrophy: Evidence for an immune pathogenesis. *Br Med J* 1980;280:1500–1503.
18. Murao S, Hirata K, Ishida T, Takahara J. Lipoatrophy induced by recombinant human insulin injection. *Intern Med* 1998;37:1031–1033.
19. Buyukgebiz A, Aydin A, Dundar B, Yorukoglu K. Localized lipoatrophy due to recombinant growth hormone therapy in a child with 6.7 kilobase gene deletion isolated growth hormone deficiency. *J Pediatr Endocrinol Metab* 1999;12:95–97.
20. Rees TD. Facial atrophy. *Clin Plast Surg* 1976;3:637–646.
21. Hodak E, David M, Sandbank M. Semicircular lipoatrophy—A pressure-induced lipoatrophy? *Clin Exp Dermatol* 1990;15:464–465.
22. Rongioletti F, Rebora A. Annular and semicircular lipoatrophies. Report of three cases and review of the literature. *J Am Acad Dermatol* 1989;20:433–436.
23. Berardinelli W. An undiagnosed endocrinometabolic syndrome: Report of two cases. *Journal of Clinical Endocrinology* 1954;14:193–204.
24. Seip M, Trygstad O. Generalized lipodystrophy, congenital and acquired (lipoatrophy). *Acta Paediatr* (Suppl) 1996;413:2–28.
25. Copeland KC, Nair KS, Kaplowitz PB, Robbins DC, Calles-Escandon J. Discordant metabolic actions of insulin in extreme lipodystrophy of childhood. *J Clin Endocrinol Metab* 1993;77:1240–1245.
26. Jaquet D, Khallouf E, Levy-Marchal C, Czernichow P. Extremely low values of serum leptin in children with congenital generalized lipoatrophy. *Eur J Endocrinol* 1999;140:107–109.
27. Pardini VC, Victoria IM, Rocha SM, Pieroni FB, Milagres G, Purisch S, Velho G. Leptin levels, beta-cell function, and insulin sensitivity in families with congenital and acquired generalized lipoatropic diabetes. *J Clin Endocrinol Metab* 1998;83:503–508.
28. Oral EA, Simha V, Ruiz E, Andewett A, Premkumar A, Snell P, Wagner AJ, DePaoli AM, Reitman ML, Taylor SI, Gorden P, Garg A. Leptin-replacement therapy for lipodystrophy. *N Engl J Med* 2002;346:570–578.
29. Foss I, Trygstad O. Lipoatrophy produced in mice and rabbits by a fraction prepared from the urine from patients with congenital generalized lipodystrophy. *Acta Endocrinol* (Copenh) 1975;80:398–416.
30. Vigouroux C, Khallouf E, Bourut C, Robert JJ, de Kerdanet M, Tubiana-Rufi N, Faure S, Weissenbach J, Capeau J, Magre J. Genetic exclusion of 14 candidate genes in lipoatropic diabetes using linkage analysis in 10 consanguineous families. *J Clin Endocrinol Metab* 1997;82:3438–3444.
31. Vigouroux C, Fajas L, Khallouf E, Meier M, Gyapay G, Lascols O, Auwerx J, Weissenbach J, Capeau J, Magre J. Human peroxisome proliferator-activated receptor-gamma2: Genetic mapping, identification of a variant in the coding sequence, and exclusion as the gene responsible for lipoatrophic diabetes. *Diabetes* 1998;47:490–492.
32. Silver K, Walston J, Plotnick L, Taylor SI, Kahn CR, Shuldiner AR. Molecular scanning of beta-3-adrenergic receptor gene in total congenital lipoatrophic diabetes mellitus. *J Clin Endocrinol Metab* 1997;82:3395–3398.
33. Garg A, Wilson R, Barnes R, Arioglu E, Zaidi Z, Gurakan F, Kocak N, O'Rahilly S, Taylor SI, Patel SB, Bowcock AM. A gene for congenital generalized lipodystrophy maps to human chromosome 9q34. *J Clin Endocrinol Metab* 1999;84:3390–3394.
34. Magre J, Delepine M, Khallouf E, Gedde-Dahl T Jr, Van Maldergem L, Sobel E, Papp J, Meier M, Megarbane A, Backy A, Verloes A, d'Abronzo FH, Seemanova E, Assan R, Baudic N, Bourut C, Czernichow P, Huet F, Grigorescu F, de Kerdanet M,

Lacombe D, Labrune P, Lanza M, Loret H, Matsuda F, Navarro J, Nivelon-Chevalier A, Polak M, Robert JJ, Tric P, Tubiana-Rufi N, Vigouroux C, Weissenbach J, Savasta S, Maassen JA, Trygstad O, Bogalho P, Freitas P, Medina JL, Bonnicci F, Joffe BI, Loyson G, Panz VR, Raal FJ, O'Rahilly S, Stephenson T, Kahn CR, Lathrop M, Capeau J, BSCL Working Group. Identification of the gene altered in Berardinelli-Seip congenital lipodystrophy on chromosome 11q13. *Nat Genet* 2001;28:365–370.

35. Agarwal AK, Arioglu E, De Almeida S, Akkoc N, Taylor SI, Bowcock AM, Barnes RI, Garg A. AGPAT2 is mutated in congenital generalized lipodystrophy linked to chromosome 9q34. *Nat Genet* 2002;31:21–23.
36. Tansey JT, Sztalryd C, Gruia-Gray J, Roush DL, Zee JV, Gavrilova O, Reitman ML, Deng CX, Li C, Kimmel AR, Londos C. Perilipin ablation results in a lean mouse with aberrant adipocyte lipolysis, enhanced leptin production, and resistance to diet-induced obesity. *Proc Natl Acad Sci USA* 2001;98:6494–6499.
37. Pages C, Simon MF, Valet P, Saulnier-Blache JS. Lysophosphatidic acid synthesis and release. *Prostaglandins Other Lipid Mediat* 2001;64:1–10.
38. Pages C, Simon M, Valet P, Saulnier-Blache JS. Lysophosphatidic acid synthesis and release(1). *Prostaglandins* 2001;64:1–10.
39. Hla T, Lee MJ, Ancellin N, Paik JH, Kluk MJ. Lysophospholipids—Receptor revelations. *Science* 2001;294:1875–1878.
40. Fang Y, Vilella-Bach M, Bachmann R, Flanigan A, Chen J. Phosphatidic acid-mediated mitogenic activation of mTOR signaling. *Science* 2001;294:1942–1945.
41. Rajab A, Heathcote K, Joshi S, Jeffery S, Patton M. Heterogeneity for congenital generalized lipodystrophy in seventeen patients from Oman. *Am J Med Genet* 2002;110:219–225.
42. Dunnigan MG, Cochrane MA, Kelly A, Scott JW. Familial lipoatrophic diabetes with dominant transmission. A new syndrome. *Q J Med* 1974;43:33–48.
43. Kobberling J, Willms B, Kattermann R, Creutzfeldt W. Lipodystrophy of the extremities. A dominantly inherited syndrome associated with lipatrophic diabetes. *Humangenetik* 1975;29:111–120.
44. Wildermuth S, Spranger S, Spranger M, Raue F, Meinck HM. Kobberling-Dunnigan syndrome: A rare cause of generalized muscular hypertrophy. *Muscle Nerve* 1996;19:843–847.
45. Garg A, Peshock RM, Fleckenstein JL. Adipose tissue distribution pattern in patients with familial partial lipodystrophy (Dunnigan variety). *J Clin Endocrinol Metab* 1999;84:170–174.
46. Garg A. Gender differences in the prevalence of metabolic complications in familial partial lipodystrophy (Dunnigan variety). *J Clin Endocrinol Metab* 2000;85:1776–1782.
47. Cao H, Hegele RA. Nuclear lamin A/C R482Q mutation in canadian kindreds with dunnigan-type familial partial lipodystrophy. *Hum Mol Genet* 2000;9:109–112.
48. Shackleton S, Lloyd DJ, Jackson SN, Evans R, Niermeijer MF, Singh BM, Schmidt H, Brabant G, Kumar S, Durrington PN, Gregory S, O'Rahilly S, Trembath RC. LMNA, encoding lamin A/C, is mutated in partial lipodystrophy [see comments]. *Nat Genet* 2000;24:153–156.
49. Speckman RA, Garg A, Du F, Bennett L, Veile R, Arioglu E, Taylor SI, Lovett M, Bowcock AM. 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;66:1192–1198.
50. Peters JM, Barnes R, Bennett L, Gitomer WM, Bowcock AM, Garg A. Localization of the gene for familial partial lipodystrophy (Dunnigan variety) to chromosome 1q21–22. *Nat Genet* 1998;18:292–295.
51. Jackson SN, Pinkney J, Bargiotta A, Veal CD, Howlett TA, McNally PG, Corral R, Johnson A, Trembath RC. A defect in the regional deposition of adipose tissue (partial lipodystrophy) is encoded by a gene at chromosome 1q. *Am J Hum Genet* 1998;63:534–540.
52. Wilson KL. The nuclear envelope, muscular dystrophy and gene expression [In Process Citation]. *Trends Cell Biol* 2000;10:125–129.
53. Heald R, McKeon F. Mutations of phosphorylation sites in lamin A that prevent nuclear lamina disassembly in mitosis. *Cell* 1990;61:579–589.
54. Clements L, Manilal S, Love DR, Morris GE. Direct interaction between emerin and lamin A. *Biochem Biophys Res Commun* 2000;267:709–714.
55. Bonne G, Di Barletta MR, Varnous S, Becane HM, Hammouda EH, Merlini L, Muntoni F, Greenberg CR, Gary F, Urtizberea JA, Duboc D, Fardeau M, Toniolo D, Schwartz K. Mutations in the gene encoding lamin A/C cause autosomal dominant Emery-Dreifuss muscular dystrophy. *Nat Genet* 1999;21:285–288.
56. Raffaele Di Barletta M, Ricci E, Galluzzi G, Tonali P, Mora M, Morandi L, Romorini A, Voit T, Orstavik KH, Merlini L, Trevisan C, Biancalana V, Housmanowa-Petrusewicz I, Bione S, Ricotti R, Schwartz K, Bonne G, Toniolo D. Different Mutations in the LMNA gene cause autosomal dominant and autosomal recessive emery-dreifuss muscular dystrophy. *Am J Hum Genet* 2000;66:1407–1412.
57. Kitaguchi T, Matsubara S, Sato M, Miyamoto K, Hirai S, Schwartz K, Bonne G. A missense mutation in the exon 8 of lamin A/C gene in a Japanese case of autosomal dominant limb-girdle muscular dystrophy and cardiac conduction block. *Neuromuscul Disord* 2001;11:542–546.
58. Brodsky GL, Muntoni F, Miocic S, Sinagra G, Sewry C, Mestroni L. Lamin A/C gene mutation associated with dilated cardiomyopathy with variable skeletal muscle involvement. *Circulation* 2000;101:473–476.
59. Morris GE, Manilal S. Heart to heart: From nuclear proteins to emery-dreifuss muscular dystrophy. *Hum Mol Genet* 1999;8:1847–1851.
60. De Sandre-Giovannoli A, Chaouch M, Kozlov S, et al. Homozygous defects in LMNA, Encoding Lamin A/C Nuclear-Envelope Proteins, Cause autosomal recessive axonal neuropathy in human (Charcot-Marie-Tooth Disorder Type 2) and mouse. *Am J Hum Genet* 2002;70:726–736.
61. Novelli G, Muchir A, Sangiuolo F, Helbling-LeClerc A, D'Apice MR, Massart C, Capon F, Sbraccia P, Federici M, Lauro R, Tudisco C, Pallotta R, Scarano G, Dallapiccola B, Merlini L, Bonne G. Mandibuloacral dysplasia is caused by a mutation in LMNA-encoding lamin A/C. *Am J Hum Genet* 2002;71:426–431.
62. Lelliott CJ, Logie L, Sewter CP, Berger D, Jani P, Blows F, O'Rahilly S, Vidal-Puig A. Lamin expression in human adipose cells in relation to anatomical site and differentiation state. *J Clin Endocrinol Metab* 2002;87:728–734.
63. Holt I, Clements L, Manilal S, Brown SC, Morris GE. The R482Q lamin A/C mutation that causes lipodystrophy does not prevent nuclear targeting of lamin A in adipocytes or its interaction with emerin. *Eur J Hum Genet* 2001;9:204–208.
64. Barroso I, Gurnell M, Crowley VE, Agostini M, Schwabe JW, Soos MA, Maslen GL, Williams TD, Lewis H, Schafer AJ, Chatterjee VK, O'Rahilly S. Dominant negative mutations in human PPARgamma associated with severe insulin resistance, diabetes mellitus and hypertension. *Nature* 1999;402:880–883.
65. 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;87:408–411.

66. Yu CE, Oshima J, Wijsman EM, Nakura J, Miki T, Piussan C, Matthews S, Fu YH, Mulligan J, Martin GM, Schellenberg GD. Mutations in the consensus helicase domains of the Werner syndrome gene. Werner's Syndrome Collaborative group. *Am J Hum Genet* 1997;60:330–341.
67. Henning KA, Li L, Iyer N, McDaniel LD, Reagan MS, Legerski R, Schultz, RA, Stefanini M, Lehmann AR, Mayne LV. The Cockayne syndrome group A gene encodes a WD repeat protein that interacts with CSB protein and a subunit of RNA polymerase II TFIIH. *Cell* 1995;82:555–564.
68. Cotton RB, Keats TE, McCoy EE. Abnormal blood glucose regulation in Cockayne's syndrome. *Pediatrics* 1970;46:54–60.
69. Petersen MB, Brostrom K, Stibler H, Skovby F. Early manifestations of the carbohydrate-deficient glycoprotein syndrome. *J Pediatr* 1993;122:66–70.
70. Schwingshandl J, Mache CJ, Rath K, Borkenstein MH. SHORT syndrome and insulin resistance. *Am J Med Genet* 1993;47:907–909.
71. Aarskog D, Ose L, Pande H, Eide N. Autosomal dominant partial lipodystrophy associated with Rieger anomaly, short stature, and insulinopenic diabetes. *Am J Med Genet* 1983;15:29–38.
72. Freidenberg GR, Cutler DL, Jones MC, Hall B, Mier RJ, Culler F, Jones KL, Lozzio C, Kaufmann S. Severe insulin resistance and diabetes mellitus in mandibuloacral dysplasia. *Am J Dis Child* 1992;146:93–99.
73. Cutler DL, Kaufmann S, Freidenberg GR. Insulin-resistant diabetes mellitus and hypermetabolism in mandibuloacral dysplasia: A newly recognized form of partial lipodystrophy. *J Clin Endocrinol Metab* 1991;73:1056–1061.
74. Breslau-Siderius EJ, Toonstra J, Baart JA, Koppeschaar HP, Maassen JA, Beemer FA. Ectodermal dysplasia, lipoatrophy, diabetes mellitus, and amastia: A second case of the AREDYLD syndrome. *Am J Med Genet* 1992;44:374–377.
75. Simha V, Garg A. Body fat distribution and metabolic derangements in patients with familial partial lipodystrophy associated with mandibuloacral dysplasia. *J Clin Endocrinol Metab* 2002;87:776–785.
76. Van Maldergem L, Bachy A, Feldman D, Bouillon R, Maassen J, Dreyer M, Rey R, Holm C, Gillerot Y. Syndrome of lipoatrophic diabetes, vitamin D resistant rickets, and persistent Mullerian ducts in a Turkish boy born to consanguineous parents. *Am J Med Genet* 1996;64:506–513.
77. Davis TM, Holdright DR, Schulenberg WE, Turner RC, Joplin GF. Retinal pigment epithelial change and partial lipodystrophy. *Postgrad Med J* 1988;64:871–874.
78. Spranger S, Spranger M, Tasman AJ, Reith W, Voigtlander T, Voigtlander V. Barraquer-Simons syndrome (with sensorineural deafness): A contribution to the differential diagnosis of lipodystrophy syndromes. *Am J Med Genet* 1997;71:397–400.
79. Berger JR, Arioglu Oral E, Taylor SI. Familial lipodystrophy associated with neurodegeneration and congenital cataracts. *Neurology* 2002;58:43–47.
80. Lawrence RD. Lipodystrophy and hepatomegaly with diabetes, lipaemia, and other metabolic disturbances: A case throwing new light on the action of insulin. Lancet 1946;I:724–731 and 773–775.
81. Hubler A, Abendroth K, Keiner T, Stocker W, Kauf E, Hein G, Stein G. Dysregulation of insulin-like growth factors in a case of generalized acquired lipoatrophic diabetes mellitus (Lawrence Syndrome) connected with autoantibodies against adipocyte membranes. *Exp Clin Endocrinol Diabetes* 1998;106:79–84.
82. Perrot H, Delaup JP, Chouvet B. [Barraquer and Simons lipodystrophy. Complement anomalies and cutaneous leukocytoclasic vasculitis]. *Ann Dermatol Venereol* 1987;114:1083–1091.
83. Biasi D, Caramaschi P, Carletto A, Bambara LM. A case of acquired partial lipodystrophy associated with localized scleroderma and undifferentiated connective tissue disease. *Rheumatol Int* 1999;19:75–76.
84. Quecedo E, Febrer I, Serrano G, Martinez-Aparicio A, Aliaga A. Partial lipodystrophy associated with juvenile dermatomyositis: Report of two cases. *Pediatr Dermatol* 1996;13:477–482.
85. Kavanagh GM, Colaco CB, Kennedy CT. Juvenile dermatomyositis associated with partial lipoatrophy. *J Am Acad Dermatol* 1993;28:348–351.
86. Sasaki T, Ono H, Nakajima H, Sugimoto J. Lipoatrophic diabetes. *J Dermatol* 1992;19:246–249.
87. Commens C, O'Neill P, Walker G. Dermatomyositis associated with multifocal lipoatrophy. *J Am Acad Dermatol* 1990;22:966–969.
88. Peters MS, Winkelmann RK. Localized lipoatrophy (atrophic connective tissue disease panniculitis). *Arch Dermatol* 1980;116:1363–1368.
89. Sissons JG, West RJ, Fallows J, Williams DG, Boucher BJ, Amos N, Peters DK. The complement abnormalities of lipodystrophy. *N Engl J Med* 1976;294:461–465.
90. McLean RH, Hoefnagel D. Partial lipodystrophy and familial C3 deficiency. *Hum Hered* 1980;30:149–154.
91. Fontaine M, Daveau M, Lebreton JP, Dumouchel L, Vannier JP, Godin M. Evidence that an autoantibody of IgG3 subclass against C3b discloses a C3 Nef activity in a pateint with partial lipodystrophy and glomerulonephritis. *Ann Immunol* (*Paris*) 1980;131C:39–53.
92. Jasin HE. Systemic lupus erythematosus, partial lipodystrophy and hypocomplementemia. *J Rheumatol* 1979;6:43–50.
93. Wakefield MA. The interrelationship between hypocomplementaemia, partial lipodystrophy and mesangiocapillary glomerulonephritis. *Postgrad Med J* 1976;52:651–652.
94. Carr A, Samaras K, Burton S, Law M, Freund J, Chisholm DJ, Cooper DA. A syndrome of peripheral lipodystrophy, hyperlipidaemia and insulin resistance in patients receiving HIV protease inhibitors. *Aids* 1998;12:F51–F58.
95. Yanovski JA, Miller KD, Kino T, Friedman TC, Chrousos GP, Tsigos C, Falloon J. Endocrine and metabolic evaluation of human immunodeficiency virus-infected patients with evidence of protease inhibitor-associated lipodystrophy. *J Clin Endocrinol Metab* 1999;84:1925–1931.
96. Viraben R, Aquilina C. Indinavir-associated lipodystrophy. *Aids* 1998;12:F37–F39.
97. Wentworth JM, Burris TP, Chatterjee VK. HIV protease inhibitors block human preadipocyte differentiation, but not via the PPARgamma/RXR heterodimer. *J Endocrinol* 2000;164:R7–R10.
98. Zhang B, MacNaul K, Szalkowski D, Li Z, Berger J, Moller DE. Inhibition of adipocyte differentiation by HIV protease inhibitors. *J Clin Endocrinol Metab* 1999;84:4274–4277.
99. Vigouroux C, Gharakhanian S, Salhi Y, Nguyen TH, Adda N, Rozenbaum W, Capeau J. Adverse metabolic disorders during highly active antiretroviral treatments (HAART) of HIV disease. *Diabetes Metab* 1999;25:383–392.
100. Vigouroux C, Gharakhanian S, Salhi Y, Nguyen TH, Chevenne D, Capeau J, Rozenbaum W. Diabetes, insulin resistance and dyslipidaemia in lipodystrophic HIV-infected patients on highly active antiretroviral therapy (HAART). *Diabetes Metab* 1999;25:225–232.
101. Christeff N, Melchior JC, de Truchis P, Perronne C, Nunez EA, Gougeon ML. Lipodystrophy defined by a clinical score in HIV-infected men on highly active antiretroviral therapy: Correlation between dyslipidaemia and steroid hormone alterations. *Aids* 1999;13:2251–2260.

102. Saint-Marc T, Partisani M, Poizot-Martin I, Rouviere O, Bruno F, Avellaneda R, Lang JM, Gastaut JA, Touraine JL. Fat distribution evaluated by computed tomography and metabolic abnormalities in patients undergoing antiretroviral therapy: Preliminary results of the LIPOCO study. *Aids* 2000;14:37–49.
103. Oral EA, Ruiz E, Andewelt A, Sebring N, Wagner AJ, DePaoli AM, Gorden P. Effect of leptin replacement on pituitary hormone regulation in patients with severe lipodystrophy. *J Clin Endocrinol and Metab* 2002;87:3110–3117.
104. Brunzell JD, Shankle SW, Bethune JE. Congenital generalized lipodystrophy accompanied by cystic angiomatosis. *Ann Intern Med* 1968;69:501–516.
105. Bjornstad PG, Semb BK, Trygstad O, Seip M. Echocardiographic assessment of cardiac function and morphology in patients with generalised lipodystrophy. *Eur J Pediatr* 1985;144:355–359.
106. Rheuban KS, Blizzard RM, Parker MA, Carter T, Wilson T, Gutgesell HP. Hypertrophic cardiomyopathy in total lipodystrophy. *J Pediatr* 1986;109:301–302.
107. Eisinger AJ, Shortland JR, Moorhead PJ. Renal disease in partial lipodystrophy. *Q J Med* 1972;41:343–354.
108. Meyrier A. The patient with glomerulonephritis and lipodystrophy. *Nephrol Dial Transplant* 1997;12:226–227.
109. Casali RE, Resnick J, Goetz F, Simmons RL, Najarian JS, Kjellstrand C. Renal transplantation in a patient with lipoatrophic diabetes. A case report. *Transplantation* 1978;26:174–177.
110. Shimomura I, Matsuda M, Hammer RE, Bashmakov Y, Brown MS, Goldstein JL. Decreased IRS-2 and increased SREBP-1c lead to mixed insulin resistance and sensitivity in livers of lipodystrophic and ob/ob mice. *Mol Cell* 2000;6:77–86.
111. Hegele RA. Premature atherosclerosis associated with monogenic insulin resistance. *Circulation* 2001;103:2225–2229.
112. Petersen KF, Oral EA, Dufour S, Befroy D, Ariyan C, Yu C, Cline GW, DePaoli AM, Taylor SI, Gorden P, Shulman GI. Leptin reverses insulin resistance and hepatic steatosis in patients with severe lipodystrophy. *J Clin Invest* 2002;109:1345–1350.
113. Unger RH. Lipotoxicity in the pathogenesis of obesity-dependent NIDDM. Genetic and clinical implications. *Diabetes* 1995;44:863–870.
114. Wang MY, Lee Y, Unger RH. Novel form of lipolysis induced by leptin. *J Biol Chem* 1999;274:17541–17544.
115. Unger RH, Zhou YT, Orci L. Regulation of fatty acid homeostasis in cells: Novel role of leptin. *Proc Natl Acad Sci USA* 1999;96:2327–2332.
116. James OF, Day CP. Non-alcoholic steatohepatitis (NASH): A disease of emerging identity and importance. *J Hepatol* 1998;29:495–501.
117. Arioglu E, Duncan-Morin J, Sebring N, Rother KI, Gottlieb N, Lieberman J, Herion D, Kleiner DE, Reynolds J, Premkumar A, Summer AE, Hoofnagle J, Reitman ML, Taylor SI. Efficacy and safety of troglitazone in the treatment of lipodystrophy syndromes. *Ann Intern Med* 2000;133:263–274.
118. Jequier E, Felber JP. Indirect calorimetry. *Baillieres Clin Endocrinol Metab* 1987;1:911–935.
119. Lillioja S, Bogardus C. Obesity and insulin resistance: Lessons learned from the Pima Indians. *Diabetes Metab Rev* 1988;4:517–540.
120. Clark CM, Jr. The National Diabetes Education Program: Changing the way diabetes is treated. *Ann Intern Med* 1999;130:324–326.
121. Meyer L, Hadjadj S, Guerci B, Delbachian I, Ziegler O, Drouin P. Lipoatrophic diabetes mellitus treated by continuous subcutaneous insulin infusion. *Diabetes Metab* 1998;24:544–546.
122. Nathan DM, Roussell A, Godine JE. Glyburide or insulin for metabolic control in non-insulin-dependent diabetes mellitus. A randomized, double-blind study. *Ann Intern Med* 1988;108:334–340.
123. Bressler R, Johnson DG. Pharmacological regulation of blood glucose levels in non-insulin-dependent diabetes mellitus. *Arch Intern Med* 1997;157:836–848.
124. Tontonoz P, Hu E, Spiegelman BM. Stimulation of adipogenesis in fibroblasts by PPAR gamma 2, a lipid-activated transcription factor. *Cell* 1994;79:1147–1156.
125. Inzucchi SE, Maggs DG, Spollett GR, Page SL, Rife FS, Walton V, Shulman GI. Efficacy and metabolic effects of metformin and troglitazone in type II diabetes mellitus. *N Engl J Med* 1998;338:867–872.
126. Maggs DG, Buchanan TA, Burant CF, Cline G, Gumbiner B, Hsueh WA, Inzucchi S, Kelley D, Nolan J, Olefsky JM, Polonsky KS, Silver D, Valiquett TR, Shulman GI. Metabolic effects of troglitazone monotherapy in type 2 diabetes mellitus. A randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 1998;128:176–185.
127. Burant CF, Sreenan S, Hirano K, Tai TA, Lohmiller J, Lukens J, Davidson NO, Ross S, Graves RA. Troglitazone action is independent of adipose tissue. *J Clin Invest* 1997;100:2900–2908.
128. Bolan C, Oral EA, Gorden P, Taylor S, Leitman SF. Intensive, long-term plasma exchange therapy for severe hypertriglyceridemia in acquired generalized lipoatrophy. *J Clin Endocrinol Metab* 2002;87:380–384.
129. Shimomura I, Hammer RE, Ikemoto S, Brown MS, Goldstein JL. Leptin reverses insulin resistance and diabetes mellitus in mice with congenital lipodystrophy. *Nature* 1999;401:73–76.
130. Yamauchi T, Kamon J, Waki H, Terauchi Y, Kubota N, Hara K, Mori Y, Ide T, Murakami K, Tsuboyama-Kasaoka W, Ezaki O, Akanuma Y, Gavrilova O, Vinson C, Reitman ML, Kagechika H, Shudo K, Yoda M, Nakano Y, Tobe K, Nagai R, Kimura S, Tomita M, Frogvel P, Kadowaki T. The fat-derived hormone adiponectin reverses insulin resistance associated with both lipoatrophy and obesity. *Nat Med* 2001;7:941–946.
131. Haque WA, Shimomura I, Matsuzawa Y, Garg A. Serum adiponectin and leptin levels in patients with lipodystrophies. *J Clin Endocrinol Metab* 2002;87:2395.
132. 2002 Online Mendelian Inheritence in Man. McKusick-Nathans Institute for Genetic Medicine, Johns Hopkins University (Baltimore, MD) and National Center for Biotechnology Information, National Library of Medicine (Bethesda, MD). Available at http://www.ncbi.nlm.nih.gov/OMIM.