

# Severe insulin resistance syndromes

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Severe insulin resistance syndromes are a heterogeneous group of rare disorders characterized by profound insulin resistance, substantial metabolic abnormalities, and a variety of clinical manifestations and complications. The etiology of these syndromes may be hereditary or acquired, due to defects in insulin potency and action, cellular responsiveness to insulin, and/or aberrations in adipose tissue function or development. Over the past decades, advances in medical technology, particularly in genomic technologies and genetic analyses, have provided insights into the underlying pathophysiological pathways and facilitated the more precise identification of several of these conditions. However, the exact cellular and molecular mechanisms of insulin resistance have not yet been fully elucidated for all syndromes. Moreover, in clinical practice, many of the syndromes are often misdiagnosed or underdiagnosed. The majority of these disorders associate with an increased risk of severe complications and mortality; thus, early identification and personalized clinical management are of the essence. This Review aims to categorize severe insulin resistance syndromes by disease process, including insulin receptor defects, signaling defects, and lipodystrophies. We also highlight several complex syndromes and emphasize the need to identify patients, investigate underlying disease mechanisms, and develop specific treatment regimens.

## Introduction

This Review, inspired by the 100th anniversary of insulin's discovery, focuses on severe insulin resistance syndromes, which constitute only the tip of the iceberg of a wide variety of clinical disorders associated with various degrees of insulin resistance. Historically, the ability to measure insulin in the circulation in the 1960s led to the realization that many subjects with diabetes and/or impaired glucose tolerance had high insulin levels, which was interpreted as a sign of resistance to the actions of insulin. Initial research efforts focused on syndromes of severe insulin resistance, to maximize impact, and also on the search for circulating antibodies against insulin or its receptor. It was soon realized that such receptors were responsible for severe insulin resistance in a minority of subjects, and thus the search continued at the molecular level with a focus on receptor and post-receptor defects.

### Insulin receptor and signaling

Insulin exerts its biological effects by binding to the insulin receptor (INSR). Since the homology between INSR and insulin-like growth factor-1 (IGF-1) receptor is high, insulin and IGF may bind and activate either receptor or the hybrid INSR/IGF-1 receptor (1–3). INSR is a cell surface heterotetrameric glycoprotein that belongs to the receptor tyrosine kinase superfamily and is composed of two extracellular  $\alpha$  subunits and two transmembrane  $\beta$  subunits linked by disulfide bridges. INSR has two isoforms, A and B, generated by alternate splicing of the mRNA. Isoform B also includes exon 11, which encodes a

12-amino acid sequence in the carboxy terminal and associates with more intense insulin binding. Conversely, isoform A, which excludes exon 11, demonstrates similar affinity for insulin and IGF-2 (1, 2). Isoform A is expressed highly during fetal development and in the brain, while isoform B is expressed in the liver. The two isoforms associate with minor downstream signaling differences (4). Ligand binding activates downstream phosphorylation events to ultimately recruit and activate receptor substrates, including the key insulin receptor substrate (IRS) and Shc proteins. The PI3K/AKT and the Ras/MAPK pathway are subsequently activated, controlling many aspects of metabolism and growth, such as cell cycle and survival functions, glycogen synthesis, and lipid synthesis (ref. 1 and Figure 1).

Abnormalities at any point of the insulin signaling pathway cascade could contribute to the pathogenesis of severe insulin resistance, though molecules upstream in the cascade have, theoretically, a more pronounced effect. Severe insulin resistance could also result from suboptimal insulin availability due to insulin molecule mutations that render insulin bioinactive or suboptimally active, albeit still immunoreactive, or from enzymatic degradation in the subcutaneous space of administered insulin.

### Definition

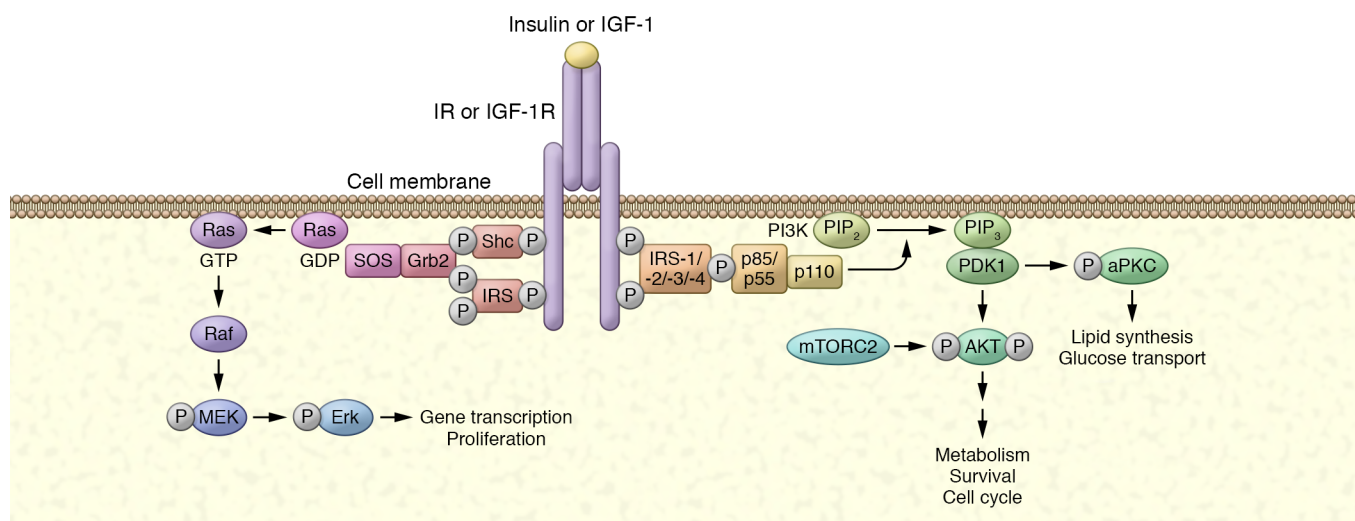
Insulin resistance is one of the most prominent metabolic disorders, in which insulin action is impaired in target tissues. It is traditionally defined as suboptimal action of a given circulating concentration of insulin to control carbohydrate metabolism (5). Since insulin has various functions in humans, compensatory hyperinsulinemia that may result from an inability to control carbohydrate metabolism usually has adverse physiological outcomes in other organs and systems. Insulin resistance thus constitutes a common underlying pathophysiological condition for many clinical disorders, usually grouped under the term “metabolic syndrome.”

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**Figure 1. Insulin and IGF-1 signaling pathways intersect.** Insulin receptor and IGF-1 receptor activation initiates a cascade of phosphorylation events. At the time of ligand binding the receptors change conformation and autophosphorylate, leading to the recruitment and phosphorylation of receptor substrates, such as IRS and Shc proteins. Shc activates the Ras/MAPK pathway, whereas IRS protein recruits PI3K to activate the PI3K/AKT pathway, leading to the generation of the second messenger PIP<sub>2</sub>. Membrane-bound PIP<sub>2</sub> then recruits and activates PDK1, which phosphorylates and activates AKT and atypical PKCs (aPKC). AKT mediates most of insulin's metabolic effects and regulates the cell cycle and cell survival. The Shc/Grb2/SOS/Ras/Raf/MAPK pathway controls cellular proliferation and gene transcription.

Severe insulin resistance syndromes are a group of rare syndromes characterized by profound insulin resistance. The prevalence of severe insulin resistance syndromes is not well documented but may reflect 0.1%–0.5% of the patients attending hospital-based diabetes clinics (6). Severe insulin resistance may be defined as a severely diminished response to insulin's biological effects, and is characterized by substantial hyperinsulinemia and impaired glucose response to endogenous and exogenous insulin. Severe insulin resistance may present with abnormal glucose homeostasis, requiring large amounts of exogenous insulin to maintain euglycemia. Notably, patients may also show hypoglycemia (especially in disorders such as Rabson-Mendenhall syndrome), which may precede hyperglycemia (6, 7).

#### Clinical features

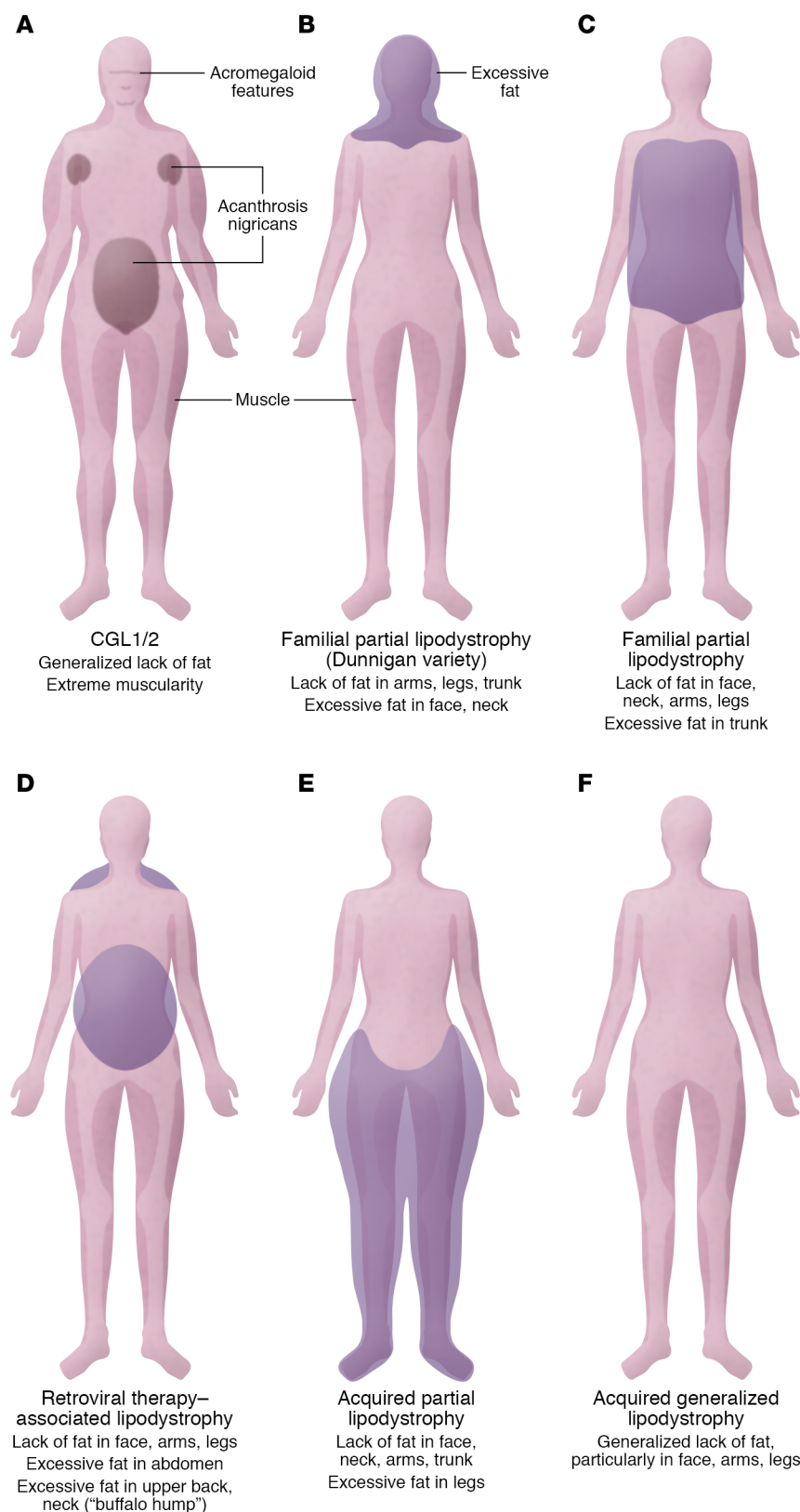
Severe insulin resistance syndromes show variable metabolic traits and diverse clinical manifestations. Identifying shared features may increase clinical awareness when considering cases of insulin resistance. Along with skin tags, acanthosis nigricans, a velvety hyperpigmented thickening of the skin, is an early sign and a common cutaneous manifestation of severe insulin resistance. The precise pathogenesis is not fully understood, but evidence suggests that high circulating insulin levels cross-react with the IGF-1 receptor on keratinocytes and dermal fibroblasts (8). Among women, ovarian dysfunction and hyperandrogenism are also common features. Hirsutism, polycystic ovaries, menstrual irregularities, or oligomenorrhea usually constitute the primary clinical manifestation in affected females. Hyperinsulinemia, in particular the synergy of insulin and gonadotropins, is implicated in the pathogenesis of polycystic ovary syndrome and ovarian hyperandrogenism (6). HAIR-AN — hyperandrogenism, insulin resistance, and acanthosis nigricans — is now considered a subphenotype of the polycystic ovary syndrome and a generic description of severe insulin resistance (6). Other

clinical features observed in some of the severe insulin resistance syndromes include dyslipidemia, namely hypertriglyceridemia; nonalcoholic fatty liver disease; adipose tissue loss; abnormal adipose topography; abnormal musculature; acromegaly features; and other growth disorders (Figure 2).

#### Diagnostic strategies

In order to determine the presence and severity of insulin resistance, several tests have been proposed. Apart from fasting glucose levels, and the mixed meal and glucose tolerance tests, fasting insulin levels above 50–70  $\mu\text{U/mL}$  or levels that exceed 350  $\mu\text{U/mL}$  after an oral glucose tolerance test may indicate severe insulin resistance (9). However, circulating insulin concentration is dynamically variable, changing over time during the evolution of diabetes. In the research setting, other techniques to assess insulin resistance include the euglycemic clamp, considered the gold standard, and the simpler intravenous glucose tolerance test, which captures up to 90% of the variability as assessed by the clamp technique (10, 11). In large-population epidemiology studies, an even simpler test, the homeostasis model assessment of insulin resistance index or the quantitative insulin sensitivity check index, can, despite limitations, evaluate insulin resistance and/or pancreatic responses. These tests may capture insulin resistance variability (up to 80% as calculated by the clamp technique) adequate for large epidemiology studies (10, 12). Importantly, no universally accepted diagnostic biochemical criteria of severe insulin resistance in the clinical setting exist.

Generally, when evaluating patients with severe phenotypes of insulin resistance, clinicians should measure and interpret fasting insulin and C-peptide in the context of circulating glucose levels. Marked hyperinsulinemia should prompt further evaluation to detect degraded insulin in subcutaneous tissue, the presence of insulin or INSR mutations, and the presence of circulating anti-IN-



**Figure 2. Patients with congenital generalized, familial partial, and acquired lipodystrophies display selective and variable adipose tissue loss.** (A) CGL1 and CGL2 may present with a generalized lack of fat, extreme muscularity, acanthosis nigricans in the groin, abdomen, or axillae, and acromegaloid features. (B) Familial partial lipodystrophy such as the Dunnigan variety may manifest as loss of fat from the trunk and upper and lower extremities and excess fat accumulation in the face and neck. (C) Other familial partial lipodystrophies are characterized by loss of fat from the face, neck, arms, and legs and excess fat accumulation in the trunk. (D) Similarly, acquired lipodystrophy associated with HIV infection may display as loss of fat from the face, arms, and legs; in certain cases, increased abdominal fat; and a "buffalo hump." (E) Acquired partial lipodystrophy is characterized by loss of subcutaneous fat from the face, neck, arms, thorax, and abdomen and simultaneously excessive amounts of subcutaneous fat in the legs. (F) Acquired generalized lipodystrophy is characterized by loss of fat from large areas of the body, particularly the face, arms, and legs.

mate the leptin levels. Clinical characteristics play a crucial role in the diagnosis; for instance, in congenital generalized lipodystrophy (CGL), the phenotype is so striking that diagnosis can be made at manifestation and/or even at birth.

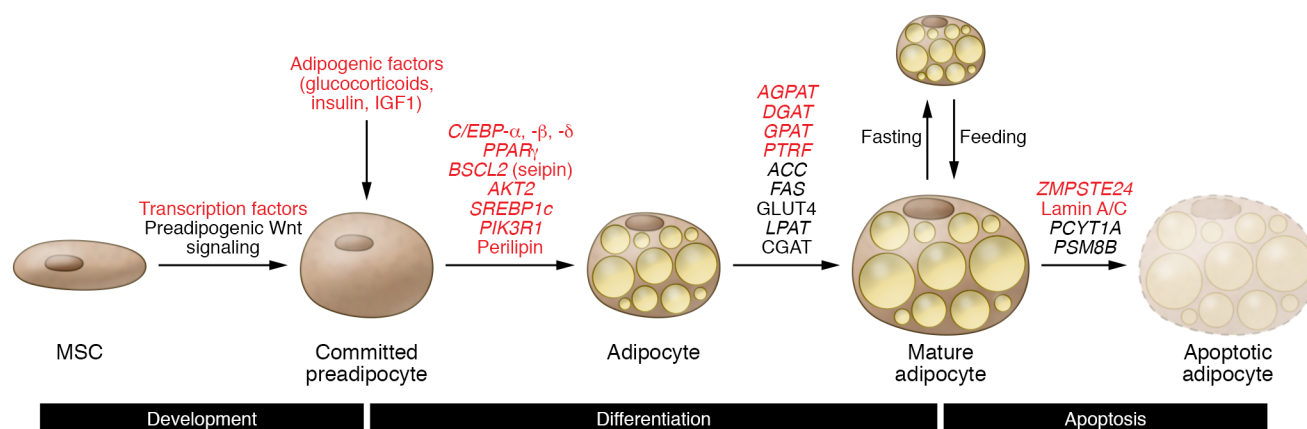
On the other hand, genetic advances have had a tremendous impact on confirmation of diagnoses for most genetic forms of severe insulin resistance. Nowadays, many facilities provide genetic testing services. However, because of the rarity of these syndromes, laboratory tests, such as those that identify anti-insulin receptor antibodies (type B insulin resistance syndrome), are generally unavailable and may require collaborating with research laboratories.

Beyond anti-insulin receptor antibodies (13), the genetic causes of severe insulin resistance include primary insulin signaling defects due to mutations and defects in the INSR gene (1), and impaired adipocyte development, apoptosis, or function (14). Advances in genetics have driven progress in the field by allowing us to identify several genes responsible for severe insulin resistance and providing an accurate diagnosis of the related

syndrome(s). Despite the rarity of severe insulin resistance syndromes, studying these diseases can provide general insights into the pathophysiological mechanisms of insulin resistance.

Notably, examination of the underlying pathophysiological mechanisms of lipodystrophies has offered essential informa-

tion. Moreover, in patients with complete lipodystrophy and potential leptin deficiency, determining leptin levels is paramount prior to initiating treatment. A specific laboratory test is required to esti-



**Figure 3. Molecular pathways implicated in adipogenesis and genes that may lead to the development of lipodystrophy.** Several molecular pathways are implicated in the development, differentiation, and apoptosis of adipocytes. The multipotent mesenchymal stem cell (MSC) serves as an adipocyte precursor. Transcription factors promote adipocyte differentiation from mesenchymal stem cells to committed preadipocytes, then to adipocytes. Preadipocytes respond to adipogenic stimuli to initiate cell differentiation to mature adipocytes. Many genes implicated in the adipocyte differentiation process are involved in the potential development of lipodystrophy (red text indicates genes or factors discussed in this Review).

tion not only regarding the management of these rather rare syndromes but also regarding other metabolic diseases, such as obesity, type 2 diabetes, and nonalcoholic fatty liver disease.

Beyond genetics, adipose tissue as an active endocrine organ produces several cytokines and bioactive mediators, such as leptin, adiponectin, and inflammatory cytokines, that regulate insulin sensitivity homeostasis, lipid metabolism, blood pressure, and inflammation (15, 16).

Ectopic fat deposition, when adipose tissue storage space is insufficient (e.g., metabolically unhealthy obesity), and/or, conversely, extreme lipodystrophy, in which adipose tissue stores are nonexistent, leads to hypoleptinemia, abnormal adiponectin levels, and insulin resistance (17–19).

Adiponectin, an adipokine abundantly expressed in white and brown adipose tissue, is inversely proportional to adipose tissue, especially centrally deposited adipose tissue (20). Adiponectin exerts a potent insulin-sensitizing action through its receptors, AdipoR1 and AdipoR2, which activate AMP-activated protein kinase (AMPK) and peroxisome proliferator-activated receptor- $\alpha$  (PPAR $\alpha$ ) signaling pathways (15, 20). Decreased adiponectin levels associate with conditions closely linked to insulin resistance, such as type 2 diabetes, hypertension, and cardiovascular disease (21–24). The adipokine leptin regulates appetite, body fat mass, metabolism, glucose homeostasis, insulin sensitivity, fatty acid oxidation, and neuroendocrine and reproductive function (25, 26). Leptin mediates its actions through several signal transduction pathways, including the Janus kinase (JAK)/signal transducer and activator of transcription 3 (STAT3) pathway, involved with energy homeostasis and possibly neuroendocrine function (15, 27). Several leptin-deficient syndromes or leptin resistance states associate with insulin resistance and diabetes (27), including severe insulin resistance in lipodystrophic subjects. Since leptin receptor and insulin receptor pathways overlap, e.g., the JAK/STAT3, AMPK, and PI3K pathways, leptin therapy may contribute to the leptin-mediated attenuation of insulin resistance directly, as well as indirectly through CNS or peripheral

actions (27). Systemic inflammation caused by proinflammatory cytokines such as TNF- $\alpha$  and IL-6 is directly correlated to the amount of adipose tissue (28). In these phenotypically severe insulin-resistant syndromes, there is chronic exposure to proinflammatory mediators, which may interrupt insulin signaling in the  $\beta$  cells of pancreatic islets and also induce insulin resistance in both liver and adipocytes (28, 29).

Understanding the regulation of adipose tissue biology in lipodystrophy has implications for understanding the pathogenesis of common disease conditions and provides the opportunity to identify metabolic pathways responsible for insulin resistance.

This Review focuses on syndromes of severe insulin resistance. The following sections discuss severe insulin resistance syndromes related to INSR signaling defects (as seen in Donohue syndrome, Rabson-Mendenhall syndrome, and type A and B syndromes) and hereditary and acquired lipodystrophies, as well as rare conditions that demonstrate features of profound insulin resistance (Supplemental Table 1; supplemental material available online with this article; <https://doi.org/10.1172/JCI142245DS1>).

## Defects of insulin signaling

### Insulin receptor defects

Mutations related to the  $\alpha$  subunit of INSR may decrease the number of available mature INSRs or the affinity of INSR for insulin binding. Furthermore, mutations related to  $\beta$  subunit tyrosine kinase domain may impair autophosphorylation, affecting the activation of downstream signaling cascades (30, 31). Genetic causes of insulin resistance from mutations in the INSR gene have been recognized in rare recessively inherited disorders including Donohue syndrome, Rabson-Mendenhall syndrome, and type A insulin resistance syndrome (1).

**Donohue syndrome.** Donohue syndrome (leprechaunism) is an extremely rare autosomal recessive disease caused by mutations in the *INSR* gene. It was first described in 1954 (32) and represents the most severe defective insulin signaling syndrome. Diagnosis is



based on genetic, biochemical, and clinical characteristics, while functional analyses try to reveal potential genotype/phenotype and structure/phenotype correlations based on the severity of *INSR* mutations (33, 34). Affected individuals seldom live beyond infancy, with most surviving less than 2 years, mainly due to intercurrent infection (6, 7, 35). While there is no known etiology, in a few cases, decreased immunoglobulin levels, mainly IgG and IgA, with intact cellular and humoral immunity, have been described (36). Normal immunoglobulin concentration, T lymphocytes, and lymphocyte proliferation have also been documented (37, 38). It is possible that impaired polymorphonuclear leukocyte bactericidal activity drives the pathophysiology (38).

**Rabson-Mendenhall syndrome.** Rabson-Mendenhall syndrome is a rare autosomal recessive disease caused by mutations in the *INSR* gene (39). Both Rabson-Mendenhall and Donohue syndromes present after birth and associate with growth and developmental defects (perhaps due to the defective mitogenic action of insulin; refs. 6, 40). Patients may present with extremely high insulin levels (41), fasting hypoglycemia (7), and failed responses to endogenous and exogenous insulin, ultimately developing refractory diabetes mellitus, severe ketoacidosis, and microvascular diabetes complications (7, 9, 41). Most individuals develop symptoms early in life but live into their 20s (1, 39). Suspected cases based on the particular clinical manifestations and laboratory findings are confirmed with genetic testing (42).

**Type A insulin resistance syndrome.** Type A insulin resistance syndrome is also a rare severe insulin resistance syndrome caused by mutations in *INSR*. Heterozygous and, in some cases, homozygous *INSR* mutations impair insulin receptor function and signal transduction (43–45). Individuals with type A insulin resistance syndrome can live beyond middle age (34). Diagnosis remains challenging, though early and accurate identification is essential for targeted treatment.

### Insulin receptor antibodies

**Type B insulin resistance syndrome.** Type B insulin resistance syndrome is an infrequent autoimmune disorder caused by polyclonal autoantibodies (usually IgG) against insulin receptors.

Experimental findings suggest that the autoantibodies act biphasically, inducing hypoglycemia in the first (acute) phase while ultimately causing hyperglycemia. The first phase associates with activation of the tyrosine kinase receptor followed by a progressive receptor downregulation and an increased degradation and subsequent reduction in cellular insulin receptors, resulting in insulin resistance and hyperglycemia (46). It has also been proposed that high autoantibody concentrations antagonize (inhibit) the *INSR*, leading to insulin resistance and hyperglycemia, while low levels partially agonize to elicit hypoglycemia (46–48). Consequently, patients exhibit profound insulin resistance and hyperglycemia, though hypoglycemia may less frequently occur.

Usually, type B insulin resistance syndrome manifests in adulthood with high 10-year mortality risk (49, 50), occurs in middle-aged women, and associates with other autoimmune conditions (such as systemic lupus erythematosus, Sjögren syndrome, and mixed connective tissue disease) or is a manifestation of an underlying malignancy, such as Hodgkin disease and myeloma (49–52).

## Lipodystrophies

Lipodystrophies are a heterogeneous group of rare disorders with approximately 1.3–4.7 cases per million (53) and even fewer for genetic lipodystrophies (54). Lipodystrophies are primarily characterized by complete or partial loss of adipose tissue and depletion of lipid storage capacity (55, 56). However, in some cases, specific body areas possess excess adipose tissue (57). In previous decades, evidence has emphasized the critical role of white adipose tissue as an active endocrine organ that efficiently stores excess energy. Based on etiology, lipodystrophy syndromes are either congenital or acquired. According to the extent of adipose tissue deficiency, we have characterized lipodystrophy syndromes as generalized or partial, such that four categories include congenital generalized lipodystrophy, acquired generalized lipodystrophy, congenital partial lipodystrophies, and acquired partial lipodystrophies. Other identified genetic causes (Figure 3) and pathophysiological pathways linked to lipodystrophy challenge the above classification (58).

Currently, no formal criteria exist. Despite progress in genetic characterization, a lipodystrophy diagnosis is based on medical history, clinical features, body composition, and metabolic status (55). Lipodystrophic syndromes are often misdiagnosed, or underdiagnosed, because of their scarcity, heterogeneity, and doctors' perceptions. Notably, many patients, especially those with generalized lipodystrophy, possess low leptin levels. Leptin participates in energy homeostasis, lipid metabolism, and insulin action (59). Despite proposed pathophysiological pathways (60), the exact mechanism by which leptin mediates clinical heterogeneity of the lipodystrophies remains unclear. Although leptin may act peripherally (white adipose tissue, liver, and muscle), affecting appetite, food intake, and lipid and glucose metabolism (60–62), the CNS likely mediates these energy-related effects (63).

The extent of adipose loss and alterations in adiposity is associated with the severity of metabolic derangements and related complications (64, 65). Metabolic disorders, and especially insulin resistance, are present in nearly all types of lipodystrophy. Additionally, more severe clinical presentation usually accompanies more severe insulin resistance. Patients can also develop severe hyperlipidemias, namely hypertriglyceridemia, inadequately controlled diabetes, progressive hepatic disease, and increased metabolic rate (66, 67).

### Congenital generalized lipodystrophy

CGL was described initially in 1954 by Berardinelli and five years later by Seip (68, 69). CGL represents rare but clinically prominent disorders with an almost complete lack of adipose presenting from birth (70).

CGL is inherited in an autosomal recessive manner with high prevalence among isolated communities or in cases of parental consanguinity (71). Until now, approximately 300 patients from different ethnic groups have been described (70, 72–76). Patients have a characteristic muscular phenotype due to a near-complete absence of adipose tissue (including subcutaneous and intra-abdominal), usually apparent at birth or during early infancy. Depending on the underlying genetic cause, CGL may spare the supportive adipose tissue such as orbits, palms, soles, and joints (77). Increased insulin levels and a hyperandrogenic state may

also contribute to prominent musculature. Other manifestations include acanthosis nigricans, acromegaly features (70, 73), mental retardation (75), polycystic ovarian syndrome, and hypertrophic cardiomyopathy (78, 79).

Individuals with CGL may develop several metabolic disorders and comorbidities, affecting women more severely (72, 73, 80). Insulin resistance may be present at an early age, even at birth. However, diabetes mellitus often develops in adolescence or early adulthood and is usually refractory to insulin therapy; ketosis is rare. Furthermore, diabetes-related complications, such as nephropathy and retinopathy, constitute a notable cause of morbidity. CGL is also associated with early-onset and progressive severe hypertriglyceridemia, leading to acute pancreatitis, fatty liver disease, and cirrhosis. Notably, individuals with CGL, regardless of age or sex, usually exhibit clinically low leptin levels (60, 81).

There are at least four molecularly distinct CGL types, with types 1 (CGL1) and 2 (CGL2) dominating the cases. *AGPAT2* and *BSCL2* gene mutations are responsible for CGL1 and CGL2, respectively. *AGPAT2* is predominantly expressed in white adipocytes (82) and involved in the acylation process of lysophosphatidic acid to phosphatidic acid, which has a crucial role in triacylglyceride and glycerophospholipid biosynthesis (83). *AGPAT2* deficiency associates with impaired signaling of critical elements such as PI3K/AKT and PPAR $\gamma$ , affecting adipogenesis and reducing the levels of stored triglycerides inside the adipose (84). At least 150 cases and 42 *AGPAT2* mutations have been published, and the number of related variants has increased over time (85, 86).

Individuals with CGL2 exhibit a more severe disease phenotype demonstrating an intense absence of body fat, including mechanical adipose depots (77). Moreover, the prevalence of diagnosed intellectual impairment is higher in patients with CGL2 (70, 75), who can develop cardiomyopathy even at a young age (78). At least 36 mutations of *BSCL2* and 167 individuals with these mutations have been described (85). The *BSCL2* gene encodes the seipin protein, which is involved in lipid droplet formation and adipocyte differentiation (74, 87). *BSCL2* participates in the biosynthesis of glycerophospholipids and triacylglycerides (83), and mutations may impair adipogenesis, the expression of enzymes (*AGPAT2*, *DGAT2*, and *lipin-1*), and lipogenic transcription factors (PPAR $\gamma$  and CCAAT/enhancer-binding protein- $\alpha$  [C/EBP- $\alpha$ ]) (88–90).

Type 3 CGL (CGL3) is linked to *CAVI* gene mutations affecting caveolin-1 function. Caveolin-1 constitutes part of the plasma membrane microdomains (caveolae), and is involved in cell migration, polarization, and proliferation (91). Caveolin-1 is also necessary for protein kinase A-mediated (PKA-mediated) phosphorylation of perilipin, which regulates lipolysis (92). Moreover, caveolin-1 loss associates with decreased de novo lipid droplet accumulation and a subsequent white adipose tissue atrophy (92). Caveolin-1 serves functional and structural roles in the biogenesis, accumulation, and metabolism of lipid droplets.

Type 4 CGL (CGL4) associates with mutations identified in the polymerase I and transcript release factor (*PTRF*) gene, also known as *CAVIN-1* (93). Cavin-1 is a peripheral membrane protein and a structural component of caveolae. Moreover, Cavin-1 regu-

lates caveolin-1 and -3 expression (93) and stabilizes and assembles the membrane structure, probably via the cytoskeleton (93, 94). Functionally, Cavin-1 modulates adipocyte differentiation and the expandability of adipose tissue (94, 95). Infants with CGL4 may show progressive body fat loss that can also include facial adipose tissue.

### Congenital partial lipodystrophies

Congenital partial lipodystrophies are a group of distinct genetic syndromes characterized by regional lipoatrophy.

**Familial partial lipodystrophies.** The majority of familial partial lipodystrophy (FPLD) syndromes are inherited in an autosomal dominant manner and demonstrate varying degrees of subcutaneous fat loss. While there are six main FPLD types, other genetic syndromes also display partial lipodystrophy characteristics, resulting in substantial genetic and phenotypic variability (58, 96, 97). The adipose fat loss usually occurs earlier in girls, and is evident during late childhood or puberty (14, 97, 98). Some clinical characteristics and metabolic derangements include insulin resistance, hyperglycemia, diabetes, acanthosis nigricans, hypertriglyceridemia, hepatic steatosis, nonalcoholic steatohepatitis, ectopic fat deposition, hyperandrogenemia, hirsutism, polycystic ovarian syndrome, reproductive dysfunction, osteoporosis, cardiomyopathy, and cardiovascular disease (97).

FPLD1, or Köbberling-type lipodystrophy, follows a polygenic inheritance pattern and is characterized by distal lipoatrophy and visceral adiposity (99, 100). Little is known about the pathological mechanisms.

FPLD2, or Dunnigan-type lipodystrophy, associates with autosomal dominant mutations of the *LMNA* gene and is the most common FPLD type (more than 500 reported cases; ref. 97). *LMNA* encodes lamin A and C proteins, which provide structural support to the nuclear envelope. Defects in these proteins may impair interaction with chromatin or other nuclear lamina proteins, leading to adipocyte apoptosis and premature death (101). Prelamin A accumulation may interfere with adipocyte transcription factors or regulators, such as sterol response element-binding protein 1 (SREBP1) and PPAR $\gamma$ , disrupting adipogenesis (101–104). Recent findings indicate that females experience a more severe disease course, due to glucocorticoid receptor GR $\beta$  overexpression or increased proinflammatory cytokine levels (105).

FPLD3 results from mutations in *PPARG*, which regulates adipocyte differentiation and function. FPLD3 is the second most common FPLD (approximately 20 families) and manifests similarly to FPLD1; however, affected patients tend to have more severe hypertriglyceridemia and hypertension (97, 106). Heterozygous mutations may attenuate gene expression or interfere directly with normal gene function (dominant negative) and inhibit adipocyte differentiation.

FPLD4 has been described in four families with autosomal dominant mutations in the *PLIN1* gene, encoding perilipin-1 (97). Perilipin-1 is the most abundant phosphoprotein in adipocytes and a principal component of lipid droplet membranes. Perilipin-1 participates in lipid storage and lipolysis by regulating hormone-sensitive lipase (HSL) and adipose tissue triglyceride lipase (ATGL), which catalyze the hydrolysis of diacylglycerol and triacylglycerol into monoacylglycerol and fatty acids (107).

FPLD5 and FPLD6 are autosomal recessive syndromes due to mutations in the cell death inducing DFFA like effector c (*CIDE*C) and lipase E, hormone sensitive type, (*LIPE*) genes, respectively. The *CIDE*C gene is involved in the differentiation of adipocytes. Moreover, *CIDE*C protein is a main regulator of lipid and glucose metabolism. It has been proposed that *CIDE*C mutations cause defects in adipocyte differentiation and the inability of lipid droplets to accumulate fat (108, 109). The *LIPE* gene encodes hormone-sensitive lipase, which associates with adipocyte function and lipid and glucose homeostasis. Pathological mutations of hormone-sensitive lipase may lead to impaired lipolysis, insulin resistance of small adipocytes, and inflammation (110).

**Mandibuloacral dysplasia.** Mandibuloacral dysplasia (MAD) is a rare autosomal recessive syndrome identified in approximately 40 cases (10, 73). It is characterized by craniofacial, skeletal, and cutaneous abnormalities, including mandibular and clavicular hypoplasia, birdlike face, joint contractures, dental anomalies, acroosteolysis, cutaneous pigmentation, and alopecia. Progeroid features and dysmorphic manifestations may be present at birth and become more prominent with age (98).

Two MAD types reflect the mutations: MAD type A is caused by mutations of the lamin A/C (*LMNA*) gene, which encodes nuclear lamina proteins. MAD type B associates with zinc metalloprotease (*ZMPSTE24*) genetic mutations and a more generalized loss of subcutaneous adipose tissue (111, 112). *ZMPSTE24* is required for posttranslational proteolytic processing of carboxy-terminal residues of prelamin A to form mature lamin A. Specifically, the prelamin A contains a carboxy-terminal cysteine that is posttranslationally modified (farnesylated) to link with the plasma membrane. Subsequently, *ZMPSTE24* catalyzes proteolytic cleavage and facilitates removal of 15 additional carboxy-terminal residues. *ZMPSTE24* mutations may lead to the accumulation of the toxic farnesylated form of prelamin A, disrupting nuclear function in several tissues (54). Some patients may experience metabolic complications such as insulin resistance, hyperinsulinemia, diabetes, and hyperlipidemia (113).

**SHORT syndrome.** SHORT syndrome (short stature; hyperextensibility of joints; ocular depression; Rieger anomaly; teething delay) associates with autosomal dominant mutations of the PI3K p85 $\alpha$  regulatory subunit 1 (*PIK3R1*) gene, which encodes the PIK3R1 protein (regulatory p85 $\alpha$  subunit; ref. 114). The p85 $\alpha$  subunit connects and stabilizes the p110 catalytic subunit, which determines its activity level (115). Both subunits form the phosphatidylinositol 3-kinase (PI3K) protein, which acts to catalyze the conversion of phosphatidylinositol phosphate 2 (PIP<sub>2</sub>) to PIP<sub>3</sub>. PIP<sub>3</sub> activates the AKT signaling pathway, which regulates cellular functions including differentiation, cell survival, and insulin's biological actions (114, 115).

#### Acquired generalized lipodystrophy

Acquired generalized lipodystrophy (AGL), or Lawrence syndrome, is a rare syndrome (approximately 80 patients) with female dominance (10, 106) and develops in patients with a negative family history, usually during childhood or adolescence (73, 116). Most patients with AGL demonstrate low leptin and markedly reduced adiponectin levels, which may associate with severe insulin resistance and related metabolic complications (117). The pathogenic mechanism is unknown. However, several cases coincided with

autoimmune or inflammatory diseases, such as panniculitis, Sjögren syndrome, juvenile-onset dermatomyositis, rheumatoid arthritis, systemic sclerosis, and systemic lupus erythematosus (116, 118, 119). Most recent findings implicate anti-adipocyte antibodies predominantly directed against perilipin-1 (120–122). It has been proposed that autoantibodies, complement activation, and proinflammatory cytokines including TNF- $\alpha$  and IL-1 contribute to AGL by impairing fat uptake, adipocyte differentiation (50, 118, 123), or adipogenesis (124) or increasing receptor-mediated apoptosis of adipocytes/preadipocytes (125, 126).

#### Acquired partial lipodystrophy

Acquired partial lipodystrophy, also known as Barraquer-Simons syndrome, is one of the most common forms of acquired lipodystrophy (10). It shows a higher prevalence in females and may follow a viral infection (127, 128). Approximately 250 cases, primarily in patients of European descent (57, 73, 129), have been reported manifesting clinical symptoms during childhood or adolescence. The etiology is still uncertain; however, autoimmune-mediated destruction of adipocytes has been proposed. Most patients possess circulating autoantibody known as C3 nephritic factor and low complement component 3 (C3) levels. Importantly, C3 nephritic factor stabilizes C3 convertase enzyme, increasing the half-life of the convertase by blocking C3 degradation, resulting in excessive C3 activation (73). Moreover, low C3 levels, circulating autoantibody called C3 nephritic factor immunoglobulin, and the presence of membranoproliferative glomerulonephritis may coincide, suggesting that inflammation plays a role (73, 130).

**Lipodystrophy in HIV patients.** The most common type of partial lipodystrophy is HIV-associated lipodystrophy syndrome (HALS), which develops in approximately 40% of patients treated with highly active antiretroviral therapy (HAART), particularly with protease inhibitors and nucleoside analog reverse transcriptase inhibitors. HALS also associates with the duration of HAART treatment (131, 132). The proposed underlying mechanisms involve increased apoptosis, impaired (pre)adipocyte differentiation (133, 134), suppressed adipogenesis (135), and altered expression of adipogenic transcription factors, including PPAR $\gamma$ , SREBP1, C/EBP- $\alpha$ , and C/EBP- $\beta$  (136). Moreover, HIV infection may inhibit adipocyte differentiation (137), while individual genetic background and inflammation processes may influence the metabolic and clinical manifestations as well as the severity of HALS (138–140). Low leptin concentration associates with reduced subcutaneous adipose tissue, while decreased adipokine levels coincide with excess visceral fat (140, 141).

The prevalence of metabolic syndrome varies, and may associate with HAART treatment duration, chronic inflammation, and the HIV infection itself. While safer HIV medications have decreased the prevalence of HALS (142), patients with HALS are also predisposed to an increased risk of atherosclerosis and cardiovascular disease (143, 144).

#### Other complex syndromes of severe insulin resistance

Other complex syndromes of severe insulin resistance are described in Supplemental Table 1. Subcutaneous insulin resistance syndrome is a rare condition characterized by profound resistance to the action of subcutaneous insulin while maintaining sensitivity to

intravenous insulin, due to increased insulin-degrading activity in the subcutaneous tissue. These patients often experience recurrent episodes of life-threatening diabetic ketoacidosis (145–147).

## Treatment strategies

Patients share common metabolic consequences of severe insulin resistance, such as diabetes, lipid abnormalities, and hepatic derangements, despite their marked phenotypic heterogeneity. Lifestyle modifications, oral and injectable antihyperglycemic medications, insulin, and lipid-lowering medications, along with therapies targeted to reverse or attenuate insulin resistance, constitute our modern treatment armamentarium.

### Diet and exercise

Aggressive lifestyle modifications focused on calorie and, when appropriate, weight reduction and increased physical activity are key elements of the therapeutic approach (148–150). Several dietary approaches, including the Mediterranean, likely contribute to maintaining a healthy weight, improving insulin resistance, and lowering inflammatory markers and endothelial dysfunction (151, 152). Moderate-intensity physical activity daily for 30 minutes is beneficial.

Lipotropic patients are typically hyperphagic, reportedly secondarily to leptin deficiency. Energy-restricted diets and caloric restriction are anecdotally effective if sustained for long periods of time (55). Most patients should follow diets with the goal of attaining ideal body weight (153), while very-low-fat diets may be appropriate in cases with severe hypertriglyceridemia. Both strength and endurance training are also encouraged (154), except in cases with cardiomyopathy (155).

### Insulin

Insulin directly or indirectly affects the function of nearly every tissue in the body. Insulin resistance is defined as a subnormal response to normal insulin concentrations. To overcome insulin resistance, exogenous insulin has been used. Patients with generalized lipodystrophy and patients with INSR mutations typically require higher insulin doses (156, 157). Since high insulin volume may result in discomfort, leakage, and impaired absorption, concentrated insulins (two or five times more concentrated than standard U-100 insulin) should be considered (158, 159).

### Insulin-like growth factor-1

Since insulin and IGF-1 mediate their effects through similar tyrosine kinase receptors, and can interchangeably activate the alternate receptor with reduced affinity, IGF-1 is a possible therapeutic agent against insulin resistance. Recombinant human IGF-1 (rhIGF-1) can improve metabolic control in INSR-related severe insulin resistance syndromes and increase life span in patients with Donohue syndrome (160, 161). RhIGF-1 can be administered subcutaneously or via continuous pump infusion (162). RhIGF-1 is thought to exercise its effects on glucose homeostasis mainly by reducing hepatic gluconeogenesis and increasing glucose uptake from peripheral tissues (163). Early treatment with rhIGF-1 typically improves outcomes, although side effects prevented its approval and wide use. Currently available publications are either single case reports or include few patients, rendering a direct comparison of treatment efficacy inconclusive.

### Insulin sensitizers

Metformin and thiazolidinediones (TZDs) play a crucial role in severe insulin resistance, improving glucose tolerance, in part by enhancing insulin sensitivity. TZDs or other PPAR $\gamma$  modulators also increase adiponectin levels. Metformin is considered first-line pharmacotherapy for improving insulin sensitivity in patients with lipodystrophies and may also improve fat redistribution in HALS (164). Several reports support the use of TZDs, particularly pioglitazone, to improve the metabolic profile in patients with partial lipodystrophy (165, 166). Only one open-label prospective study tested the troglitazone efficacy (167). Consequently, TZDs need to be used cautiously in patients with generalized lipodystrophy. Similarly, incretin-based therapies including glucagon-like peptide 1 receptor agonists and sodium glucose transporter inhibitors can be used in lipodystrophy, but their efficacy has not been studied systematically.

### Lipid-lowering medications

Hyperlipidemia is usually managed with statins, fibrates, and fish oil, rich in omega-3 fatty acids (168, 169). No systemic studies have tested the efficacy of lipid-lowering medications in these patient populations. Combination of fibrates with statins should be used cautiously given the cumulative risk of myopathy and hepatotoxicity. Fibrates and/or long-chain omega-3 fatty acids may be considered for high triglycerides. Additional LDL-cholesterol-lowering medications, such as ezetimibe and PCSK9 (proprotein convertase subtilisin/kexin type 9) antibody inhibitors, are available, though they have not been studied specifically in this patient population. Inclisiran, a small interfering RNA, which may provide sustained LDL reductions, is a promising nonantibody approach that targets PCSK9. The efficacy of inclisiran has been demonstrated in the most recent phase III trials among patients with atherosclerotic cardiovascular disease or its equivalent and elevated LDL level (170). Several liver-specific secreted proteins have been identified as playing a key role in regulating lipid metabolism. Bempedoic acid, an inhibitor of ATP citrate lyase, alone or in combination with statin or ezetimibe, may prove beneficial (171). In 2020, bempedoic acid was approved by the FDA for heterozygous familial hypercholesterolemia. Volanesorsen is a second-generation apolipoprotein C-III antisense oligonucleotide that decreases apolipoprotein C-III, a major triglyceride regulator, and subsequently reduces triglyceride levels (172, 173). The BROADEN Study (174), a randomized, double-blind, placebo-controlled study, recruited patients with partial lipodystrophy and hypertriglyceridemia and will report the effect and safety profile of volanesorsen. Similarly, trials involving angiopoietin-like 3 (ANGPTL3) inhibition via antibodies, such as evinacumab, or antisense oligonucleotides may reveal additional targets for the treatment of hypercholesterolemia in lipodystrophy patient populations (175, 176). Gemcabene is another agent that can enhance the clearance of VLDL-cholesterol, increasing HDL and decreasing hepatic triglyceride synthesis. A clinical study of gemcabene for the management of hypertriglyceridemia and nonalcoholic fatty liver disease in familial partial lipodystrophy patients is ongoing (177).



### Etiologic therapeutic strategies

**Leptin therapy.** Metreleptin, a leptin analog, is the only drug specifically indicated for the treatment of lipodystrophy in the United States (178). In multiple prospective, albeit small and uncontrolled, studies of generalized lipodystrophy, metreleptin treatment suppressed appetite and favored metabolic profiles compatible with reducing, or even discontinuing, antidiabetic medications. Further, nonalcoholic steatohepatitis improved (179–181). In patients taking metreleptin, improved peripheral glucose disposal, hepatic glucose output, and insulin secretion lowered fasting glucose levels (182). Within weeks, triglyceride levels decreased, achieving 60% reduction after one year of treatment (66). Metreleptin has also found off-label use in partial lipodystrophy (183), with possible effectiveness in pediatric patients (184); however, the possibility of developing anti-leptin neutralizing antibodies has prompted the FDA to prevent metreleptin use for any lipodystrophies except complete lipodystrophy (185). While T cell lymphoma has been reported in individuals with acquired lipodystrophy who were treated with metreleptin, it remains unclear whether the cases represented a treatment side effect or a natural history of disease progression (186).

**GHRH analog.** The growth hormone-releasing hormone (GHRH) analog tesamorelin has FDA approval for use in HALS, in which it improves metabolic abnormalities associated with visceral fat accumulation (187, 188). Tesamorelin is administered as a subcutaneous injection daily. Several randomized clinical trials reported visceral fat reduction during treatment (189, 190), but rapid reaccumulation was noted after discontinuation of therapy. The possibility that tesamorelin worsens glucose intolerance through increased IGF-1 levels warrants caution (191).

**Immunosuppressants.** Type B insulin resistance is traditionally challenging to manage and has been treated with various forms of immunosuppression with mixed success (192). Malek et al. reported a protocol of rituximab, cyclophosphamide, and pulse steroids (49), which achieved remission in seven patients with type B insulin resistance. However, after about eight months immunosuppressive therapy was stopped and insulin resistance

status remained unclear. Complementary strategies to eliminate the culprit antibody may account for the success. Cyclosporin A, azathioprine, intravenous immunoglobulins, and plasmapheresis have also been used with variable effects (193).

### Cosmetic surgery

Cosmetic surgery has been effective in correcting hypo- or hypertrophic depots in patients with lipodystrophy, with positive psychological implications (55). However, this approach should ideally be coupled with modifications as outlined above.

### Conclusion

This Review has discussed the pathogenesis and features of several severe insulin resistance syndromes and potential therapeutic interventions. Studying these rare conditions has historically opened new pathways in diabetes research and allowed us to gain important insights into insulin's action and physiology.

### Author contributions

All authors contributed to the conception and design of the overall commissioned work. This process was chaired by CSM. All authors were involved in the drafting and revision of the report. AMA and AF led the drafting and editing process. All authors approved the final version for publication and agree to be held accountable for resolving any future questions related to the integrity or accuracy of the work.

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