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Syndromic insulin resistance: Models for the therapeutic basis of the metabolic syndrome and other targets of insulin resistance

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Abstract

Objective—Insulin resistance is the key feature of the "metabolic syndrome," a cluster of risk factors for cardiovascular disease and diabetes that includes hypertension, dyslipidemia, obesity, and hyperglycemia. Existing treatments target individual metabolic syndrome components, and act non-specifically with respect to disease pathophysiology. Our goal is to understand the link between insulin resistance and the metabolic syndrome, and how to develop treatment approaches.

Methods—We present three cases of extreme, syndromic insulin resistance: lipodystrophy, autoantibodies to the insulin receptor, and mutations of the insulin receptor, with discussion of pathophysiology and treatment.

Results—In lipodystrophy, insulin resistance is a direct consequence of leptin deficiency, and thus leptin replacement reverses metabolic syndrome abnormalities, including diabetes and hypertriglyeridemia. The insulin "receptoropathies", including autoantibodies to the insulin receptor and insulin receptor mutations, are characterized by extreme insulin resistance and ovarian hyperandrogenism, without dyslipidemia or fatty liver disease. Autoantibodies to the insulin receptor can be treated using an immunosuppressive paradigm adapted from treatment of other autoimmune and neoplastic conditions. Leptin treatment has shown some success in treating hyperglycemia in insulin receptor mutations. Treatment for this condition remains inadequate, and novel therapies that bypass insulin receptor signaling, such as enhancers of brown adipose tissue, are needed.

Conclusion—We presented a clinical approach to treatment of syndromic insulin resistance. The study of rare diseases that replicate the metabolic syndrome, with clear-cut pathophysiology, allows the opportunity to understand novel physiology, and develop targeted therapies that may be applicable to the broader population with obesity, insulin resistance, and diabetes.

Keywords

Insulin resistance; Metabolic syndrome; Lipodystrophy; Leptin; Type B insulin resistance; Insulin receptor mutation

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Introduction

The prevalence of obesity has reached epidemic proportions and the incidence and economic burden of obesity-related complications are rapidly increasing [1-3]. Adult obesity in the United States has more than doubled from 15% in the late 1970's to 35.7% in 2010[4]. Even more alarming, over the same period, the prevalence of adolescent obesity has tripled from 5% to 17%[4]. In parallel with the rise in obesity, the incidence of type 2 diabetes has risen, with a current prevalence rate of 8.3% of US adults[5]. The prevalence in children is less well established, but appears to be dramatically rising. The 1999-2002 NHANES survey estimated 39,005 US adolescents currently living with T2DM, or 4.1 per 1000[6].

Type 2 diabetes results from a combination of insulin resistance (usually associated with obesity) and relative insulin deficiency. Insulin resistance is the key pathophysiologic feature of the "metabolic syndrome," a cluster of independent epidemiologic risk factors for cardiovascular disease and diabetes. The metabolic syndrome was first described by Reaven in 1988[7], and includes hypertension, dyslipidemia (elevated triglycerides and low HDL cholesterol), central adiposity, and elevated fasting glucose[8]. Specific etiologies for these risk factors are typically found in less than 10% of cases. For example, in hypertension, a minority of cases are due to monogenic ion channel mutations (e.g. Liddle syndrome), endocrine abnormalities (e.g. hyperaldosteronism), or vascular abnormalities (e.g. renal artery stenosis), while the majority is termed "essential," with no clear pathophysiologic basis. Similarly, dyslipidemia is infrequently due to a defined cause, such as LDL receptor abnormalities in familial hypercholesterolemia. The same is true for diabetes, for which rare cases can be attributed to defined abnormalities of the insulin receptor, or defects in beta-cell transcription factors or machinery. The quest in the common metabolic syndrome is to find a unifying mechanism that joins these diverse risk factors, and could provide a unique therapeutic target.

The gold standard by which endocrinologists practice medicine

Therapies for most metabolic syndrome features exist, and have been proven effective using the gold standard of evidence-based medical practice: randomized, controlled trials. Pharmacologic therapies to treat hypertension arose first, with clinical trials from the 1960's demonstrating reduced morbidity. In the 1980's clinical trials of cholesterol lowering medications changed medical practice, demonstrating that cholesterol lowering, particularly of LDL using HMG-CoA reductase inhibitors (statins), reduced mortality and cardiovascular events. It wasn't until 1993 that the Diabetes Control and Complications Trial (DCCT) definitively demonstrated benefit of blood glucose lowering to prevent microvascular complications of type 1 diabetes[9]. The follow-up study to the DCCT, the Epidemiology of Diabetes Interventions and Complications (EDIC) study, showed possible benefit of intensive insulin therapy on macrovascular disease, as well[10]. This paradigm shift was dependent on the development of several new technologies, including home blood glucose monitoring, the use of hemoglobin A1c as a measure of chronic glycemia control, and improved methods of insulin delivery[11]. Results of the United Kingdom Prospective Diabetes Study (UKPDS) conveyed a similar message for treatment of type 2 diabetes[12, 13].

It is important to consider that, with the exception of insulin therapy for type 1 diabetes, all of the above treatments (antihypertensive medications, statins, and oral hypoglycemic agents) act in a non-specific manner with respect to disease pathophysiology. Our ultimate goal in medicine is to understand the pathophysiologic basis of disease, thus allowing targeted pharmacotherapy. The study of rare diseases that replicate the metabolic syndrome or its components, in the context of clear-cut pathophysiology, allows us the opportunity to both understand novel physiology, and develop targeted therapies that may be applicable to

the broader population with prevalent obesity, insulin resistance, and diabetes. In the present commentary, we will describe patient examples where specific targeted therapeutic approaches have been used. The examples will include, (a) the development of new technology, (b) new use of existing technology, and (c) combining existing technology with proposed new technology.

Development of new technology: Leptin treatment in lipodystrophy

Clinical vignette

A fourteen year old Caucasian female presented with generalized lack of subcutaneous adipose tissue, insulin resistance and diabetes, severe hypertriglyceridemia (10,000-12,000 mg/dL), eruptive xanthomas, and recurrent pancreatitis (Figure 1). She required three times weekly plasmapheresis for management of hypertriglyceridemia. She was also found to have steatohepatitis, amenorrhea, and hypertrophic cardiomyopathy. After the diagnosis of acquired generalized lipodystrophy was established at National Institute of Health, she became the first lipodystrophic patient to be treated with leptin replacement. Over the past 11 years she has been on leptin therapy (Metreleptin, the pharmaceutical form of leptin, which is composed of 146 amino acids of mature human leptin with an additional methionyl residue at the N-terminal end of the recombinant protein) and her metabolic profile has significantly improved, with marked reduction in her insulin requirements, hypertriglyceridemia, and hepatic steatosis, resolution of the eruptive xanthomas and recurrent pancreatitis. She is now 28 years old, married and is living an active, productive life.

Leptin: From hormone to pharmaceutical

Leptin was the first adipokine, or adipocyte-derived hormone, to be discovered. This discovery heralded a new understanding of adipose tissue as not merely a passive energy storage depot, but an active endocrine organ. The discovery of leptin derived from a spontaneously occurring mouse model of obesity, the ob/ob mouse. Through positional cloning, the laboratory of Jeffry Friedman identified the causative gene responsible for obesity in this animal[14]. The ob gene product was christened leptin, derived from the Greek word "leptos," meaning thin. When ob/ob mice were given leptin replacement, they became lean, primarily through reduction in appetite[2, 6]. Unfortunately, leptin did not prove to be the hoped-for "magic bullet" treatment for obesity, because obese individuals have high endogenous leptin levels[15] as a function of increased body fat, and do not respond to exogenously administered leptin[16]. This is analogous to the hyperinsulinemia observed in insulin resistant states. After its failure in common obesity, leptin therapy was tried in humans with obesity secondary to leptin gene mutations, an extremely rare disorder that is essentially the human equivalent of the ob/ob mouse[17]. Like the mice, these leptin-deficient individuals proved to be extremely sensitive to leptin's appetite-suppressing effects, experiencing dramatic weight loss, coupled with normalization of other endocrine and non-endocrine abnormalities[18].

Leptin treatment was subsequently tested in another condition associated with leptin deficiency: lipodystrophy. The term lipodystrophy refers to a heterogeneous group of disorders characterized by partial or complete loss of adipose tissue. Table 1 summarizes the clinical features common to the various forms of lipodystrophy, and Table 2 distinguishes among lipodystrophy subtypes. Because leptin is made in adipocytes, lipodystrophic patients, who have deficient subcutaneous adipose tissue, have very low leptin levels. Analogous to the mouse model of congenital leptin deficiency, mouse models of lipodystrophy proved to be responsive to leptin treatment[19, 20]. The first patient with lipodystrophy was treated with leptin beginning in 2000, with the dramatic clinical results

described in the vignette, above. In the 12 years since, leptin replacement in lipodystrophy has been demonstrated to reduce food intake by half[21, 22] and ameliorate most metabolic abnormalities, including insulin resistance[22-24] and diabetes[23, 25, 26]. Leptin replacement in lipodystrophy reduces hypertriglyceridemia[24-26] and lowers LDL cholesterol, but does not change HDL[25]. In addition, it reduces ectopic lipid storage, including reductions in muscle and liver triglyceride[27], as well as improved non-alcoholic steatohepatitis (NASH) pathologic scores[22, 28]. Leptin also normalizes reproductive status both by reducing the ovarian hyperandrogenism caused by insulin resistance[29], and by restoring the ultradian rhythm of luteinizing hormone secretion (demonstrated in congenital leptin deficiency and hypothalamic amenorrhea)[18, 30]. These effects are consistent in all variants of lipodystrophy studied[25], and have been sustained throughout long-term leptin treatment[31].

Lipodystrophy as model for human metabolic syndrome

Eighty percent of patients with lipodystrophy meet clinical criteria for the metabolic syndrome[32]. A comparison of features of lipodystrophy versus obesity is shown in Table 3. In the common form of the metabolic syndrome, the basis for the cluster of insulin resistance, diabetes, and dyslipidemia is unclear, and therapy is directed at each component. By contrast, in patients with lipodystrophy, leptin deficiency represents a common etiologic factor that explains the metabolic defects of insulin resistance and dyslipidemia. The logical corollary to this is that leptin replacement in this population represents a common therapeutic target that can correct these defects.

The mechanism by which leptin deficiency causes insulin resistance has not been well established, but likely shares many common pathways with obesity-associated insulin resistance. Ectopic lipid accumulation within the liver is clearly important in both obesity and lipodystrophy, and is associated with hepatic insulin resistance. Accumulation of intramyocellular diacylglycerol (also present in both obesity and lipodystrophy) can cause activation of atypical protein kinase C isoforms, leading to muscle insulin resistance[33]. Additional mechanisms include activation of the unfolded protein response (aka, endoplasmic reticulum stress), inflammation, and mitochondrial dysfunction[33].

Just as there exist common mechanisms for insulin resistance in obesity and lipodystrophy, there exists a common treatment modality for insulin resistance in these two conditions. This treatment is reduction of energy storage. This is clearly very challenging to accomplish, and may be achieved by reducing energy intake (e.g. via dieting or bariatric surgery), and/or by increasing energy expenditure via exercise. In lipodystrophy, treatment with leptin reduces caloric intake by ~50%, and this caloric restriction is likely a major mediator of leptin's clinical benefits. However, leptin-induced improvements in insulin resistance and glycemia occurring independent of food intake have been demonstrated in rodents[19, 34-37], and, to some extent, in humans[26].

New use of existing technology: Autoantibodies to the insulin receptor

Clinical Vignette

A twenty year-old African-American woman presented to National Institutes of Health with extreme insulin resistance and diabetes, with an average fasting blood glucose of 371 mg/dL and glycated hemoglobin levels ranging between 12-20% despite 18,000 units of insulin daily. She had a history of a 35 lbs weight loss on a 3500 kcal /day diet, massive polyuria (up to 15 liters of urine daily), and severe acanthosis nigricans. She was the first patient who was treated for autoantibodies to the insulin receptor (also called Type B insulin resistance) using a 3-pronged approach with rituximab, cyclophosphamide, and pulsed steroids. She has been in remission for the past 4 years.

Autoantibodies to the Insulin Receptor

Type B insulin resistance is caused by circulating autoantobodies to the insulin receptor. The resultant lack of insulin signaling causes extreme insulin resistance and hyperglycemia that is refractory to very large doses of exogenous insulin (up to 18,000 units daily, as described in the vignette). Hypoglycemia is an occasional symptom, thought to be associated with low-titer antibodies with partial agonist effects. Other major presenting features of this disease are acanthosis nigricans, severe hyperandrogenism, and weight loss; additional laboratory features include low triglycerides and high adiponectin levels. This condition is frequently associated with autoimmune and rheumatologic diseases, such as lupus and Sjogren syndrome, or it can be part of a paraneoplastic syndrome. Although some patients may undergo spontaneous remission, the mortality rate is generally high and treatment has been challenging[38].

Immunologic Therapy for Autoantibodies to the Insulin Receptor

While high doses of immunosuppressive drugs used to treat conditions such as lupus nephritis can also resolve autoantibodies to the insulin receptor[39], these treatments are also extremely toxic. In 2010, our group reported successful treatment of seven patients using a three-pronged approach (Figure 2), with the goal of eliminating the autoantibody to the insulin receptor[40]. First, rituximab, an antibody against CD-20, a cell surface molecule expressed by B-cell progenitors, was used to target antibody-producing B lymphocytes. Second, pulsed steroids were used to target the pre-existing antibody-producing plasma cells. Third, a low dose of an immunosuppressive drug, (either cyclophosphamide or cyclosporine for neutropenic patients) was used to achieve non-specific B- and T-cell function suppression. This treatment protocol evolved out of available treatments for other autoimmune or neoplastic conditions.

Autoantibodies to the insulin receptor are representative of a class of disorders caused by pathogenic antibodies to cell-surface receptors, and thus the concept of multifaceted immunosuppression may be applicable to other endocrine and non-endocrine conditions with similar pathophysiology. Examples of such conditions are Graves disease (TSH receptor antibodies), myasthenia gravis (acetylcholine receptor antibodies), ovarian failure (gonadotropin receptor antibodies), iron deficiency anemia (transferrin receptor antibodies), hypoparathyroidism (antibodies against the parathyroid hormone or calcium sensing receptors), and even occasional forms of obesity due to melanocortin 4 receptor antibodies[41-45]. In addition, this treatment approach might be broadened to target autoantibodies against circulating hormones, such as insulin antibodies in the insulin autoimmune syndrome. In this syndrome, autoantibodies against circulating insulin produce hypoglycemia[46, 47]. Preliminary studies suggest that the general therapeutic protocol described above may be applicable to the insulin autoimmune syndrome. Depending on the severity of the patient's condition, all three arms of this treatment regimen may not be necessary; in less severe cases, only one or two components may be adequate.

Combining old and new technologies: Insulin receptor mutations

Clinical Vignette

Two siblings with the Rabson-Mendenhall syndrome due to homozygous insulin receptor mutations initially presented at age 3 to 4 years with a history of hypoglycemia, growth retardation, and acanthosis nigricans. By age 7 and 9 years they were found to have severe hyperinsulinemia and diabetes. The diabetes was initially managed by oral hypoglycemic agents (metformin and rosiglitazone, and insulin was later added to the male patient's regimen at age 12 years. Severe hyperandrogenism and hirsutism were also present in the female patient. These two patients were the first patients with insulin receptor mutations to

be treated with leptin, beginning at age 11 and 13 years. After 10 months of leptin treatment, the fasting blood glucose decreased by 60 % in the female and by 40 % in the male. The male's insulin requirement was reduced from 300 to 200 units daily. Both patients showed a reduction in hemoglobin A1C and fasting insulin. After withdrawal of leptin for three months, all glycemic parameters returned to, or were worse than, the baseline values[48].

Insulin Receptor Mutations

Insulin receptor mutations are characterized by extreme forms of insulin resistance. Like type 2 diabetes, the initial hyperinsulinism becomes attenuated over time through loss of beta cell function, and overt diabetes ensues. Patients with insulin receptor mutations are subject to all of the attendant microvascular complications of diabetes, and early mortality may occur in late childhood or young adulthood[49]. In its most severe form, called Donohue syndrome or leprechaunism, death occurs prior to age two years[49]. Prior attempts at treatment have involved the use of concentrated (U-500) insulin in an attempt to ameliorate the degree of hyperglycemia, but this has met with limited success. Oral agents such as metformin have some added benefit, but overall, treatment for this condition is inadequate.

New Use of an Existing Technology: Leptin treatment in Insulin Receptor Mutations

Because treatment of patients with insulin receptor mutations with high-dose insulin has only limited efficacy, it is critical to consider treatment strategies that bypass the insulin receptor. Leptin treatment for patients with insulin receptor mutations was initiated based on the observation that the signal transduction cascades downstream of the insulin and the leptin receptors overlap at the level of phosphoinositide (PI) 3-kinase. It was therefore hypothesized that treatment with exogenous leptin might increase post-receptor insulin signaling downstream of PI 3-kinase. Although some efficacy of leptin in lowering blood glucose has been observed in these patients, it has not been possible to demonstrate whether this improvement was, indeed, mediated via increased post-insulin-receptor signaling, as hypothesized.

Potential new approaches to treatment of insulin receptor mutations

Even with leptin therapy, management of diabetes in patients with insulin receptor mutations remains inadequate, and additional, novel treatments for this condition are needed. One potential target is activation of brown adipose tissue. One well known activator of brown adipose tissue is thyroid hormone, and a single patient observation suggests that this mechanism may be relevant for patients with insulin receptor mutations[50]: A patient with homozygous mutation of the insulin receptor was started on suppressive doses of levothyroxine for treatment of thyroid cancer. Over the subsequent 30 months, she had remarkable improvement in her glycemia control, with a decrease in hemoglobin A1c from 9.9 to 5.5%, despite tapering of insulin from 3000 to 0 units per day, and discontinuation of metformin. Positron emission tomography demonstrated the presence of brown adipose tissue, which was confirmed on biopsy. During withdrawal of levothyroxine, the brown adipose tissue diminished, and glycemia control worsened, supporting the hypothesis that high-dose levothyroxine mediated the improvements in blood glucose via brown adipose tissue. Importantly, the patient's insulin sensitivity (assessed via the gold-standard hyperinsulinemic, euglycemic clamp technique) did not change in the presence or absence of suppressive levothyroxine, suggesting that the improvements in glycemia occurred independent of insulin signaling through its receptor.

Additional activators of brown adipose tissue have been suggested based on rodent data. Fibroblast growth factor 21 (FGF21) mediates direct activation of brown fat thermogenesis during the fetal-to neonatal transition[51]. Mice that are deficient in FGF21 have diminished "browning" of white adipose tissue and have an impaired ability to adapt to chronic cold

exposure[52]. Transcriptional activators, like PPAR-α in the liver and PPAR-γ in adipocytes control expression of FGF21. Transgenic mice overexpressing FGF21 in the liver have increased insulin sensitivity, glucose clearance, decreased plasma triglyceride, increased fat utilization and energy expenditure [53, 54]. The protein irisin is another activator of brown adipose tissue in rodents[55]. Production of this protein is enhanced in response to the exercise-induced rise in the transcriptional co-activator PPAR-γ co-activator-1 α (PGC1-α). Mice that overexpress irisin develop browning of white adipose tissue, and have improved glucose tolerance after high-fat diet feeding. Neither FGF-21 nor irisin have been studied in humans, but, because they improve glucose homeostasis independent of insulin-receptor signal transduction, they may have potential therapeutic roles for management of diabetes in patients with insulin receptor mutations.

Lessons Learned from Syndromic Insulin Resistance as Models for the Metabolic Syndrome

Several lessons can be derived from these clinical studies of rare, syndromic forms of insulin resistance. It is clear that the common metabolic syndrome, lipodystrophy, and insulin receptor mutations are all characterized by varying degrees of insulin resistance (Table 4). Furthermore, the hyperinsulinemia in these conditions is sufficient to cause polycystic ovarian syndrome and hyperandrogenism[56]. However, the other phenotypic features of these conditions cannot be derived from insulin resistance, per se. For example, in the common metabolic syndrome and lipodystrophy, triglycerides are elevated, while in insulin receptoropathies, triglyceride levels are low[57]. This demonstrates that, in order to stimulate lipid synthetic pathways in the liver, the insulin receptor is required. Thus, ectopic fat can only be generated in the common metabolic syndrome and in lipodystrophy, and does not occur in insulin receptoropathies despite extreme insulin resistance. In addition, and paradoxically, the insulin receptoropathies are characterized by high adiponectin[58, 59], as contrasted to the low adiponectin levels observed in the common metabolic syndrome and lipodystrophy. Again, this suggests that intact signaling through the insulin receptor is required for the low adiponectin levels typically seen with insulin resistant states.

In the insulin receptoropathies, the mechanism of insulin resistance is clear – the failure of insulin to activate its receptor, and hence, downstream signal transduction cascades. The mechanism of insulin resistance in lipodystrophy clearly involves leptin deficiency, but the downstream effectors of leptin deficiency are complex, and likely overlap with common, obesity-associated insulin resistance. There is a common conundrum in lipodystrophy and obesity about the inciting event leading to insulin resistance. For instance, mitochondrial dysfunction has been proposed as a mechanism leading to insulin resistance, but it may also be a consequence of insulin resistance, as shown in patients with insulin receptor mutations[60]. Thus, we continue to face the conundrum of the initial event leading to insulin resistance in the common metabolic syndrome.

Conclusions

The clinical endocrinologist has responsibility for several of the world's most prevalent and debilitating chronic diseases. The public cost of these diseases in both fiscal and social terms is enormous. All available technologies, including genomics, epidemiology, developmental science, and model systems will be needed in the pursuit of effective prevention and treatment. We have offered a clinical approach using disease models that have been informative for both developing therapeutic and conceptual approaches to certain rare diseases, but which may also be informative for the serious common diseases associated with metabolic dysfunction.

Acknowledgments

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Figure 1.
A) Patient with acquired generalized lipodystrophy prior to treatment, demonstrating generalized paucity of subcutaneous fat, eruptive xanthomas, and protuberant abdomen due to enlarged fatty liver. Additional presenting features included insulin resistance and diabetes, severe hypertriglyceridemia, and recurrent pancreatitis. B) The same patient after one year of leptin therapy, demonstrating resolution of eruptive xanthomas, and a significant decrease in liver volume. She also had significant improvement in diabetes and hypertriglyceridemia, with resolution of pancreatitis.
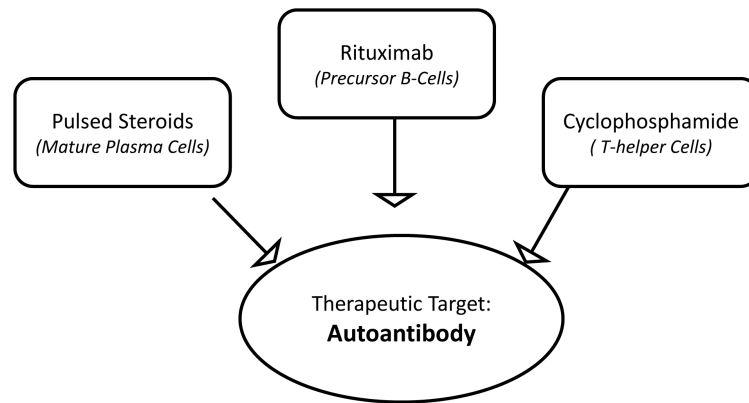
Figure 2.
Therapeutic strategy for Type B insulin resistance caused by autoantibodies to the insulin receptor. Elimination of the autoantibody is the goal for this three-pronged approach. Rituximab, an antibody against CD-20, a cell surface molecule expressed by B-cell progenitors, targets antibody-producing B lymphocytes. Pulsed steroids target the pre-existing antibody-producing plasma cells. Non-specific B- and T-cell function suppression is achieved by a low dose immunosuppressive drug, either cyclophosphamide or cyclosporine.

Table 1

Phenotypic features of patients with lipodystrophy

Paucity of fat
Deficiency of adipocyte hormones (e.g. leptin)
Insulin resistance
Acanthosis nigricans
Severe hypertriglyceridemia and resultant recurrent pancreatitis
Fatty infiltration of the liver and Non-alcoholic Steatohepatitis
Features of Polycystic Ovarian Syndrome
Low High-Density Lipoprotein Cholesterol

Table 2

Lipodystrophy subtypes that have been treated with leptin[61, 62].

	Inheritance (Genes)	Leptin level range (ng/mL)	Phenotype and distinct features
Congenital Generalized Lipodystrophy (CGL)	Autosomal recessive (AGPAT2 Seipin)	0.31-3.32	Near-total lack of body fat and muscular appearance at birth, acanthosis nigricans, umbilical prominence/hernia, primary amenorrhea in females, hirsutism, hypertrophic cardiomyopathy, and polycystic ovaries. Absence of mechanical fat in palms and soles in seipin mutations. Focal lytic lesions in the appendicular bones in AGPAT2 mutations.
Familial and Acquired Partial Lipodystrophy (FPL)	Autosomal dominant (LMNA, PPARγ, Unknown)	0.95-14.1	Normal fat distribution at birth and during early childhood. Development of abnormal subcutaneous fat distribution during late childhood and adolescence; usually absence of subcutaneous fat in limbs but abundance of fat around the neck and face, occasionally over pubic area or axillae and intra-abdominal region.
Acquired Generalized Lipodystrophy (AGL)	–	0.36-3.95	Born with normal fat, start to lose subcutaneous fat in childhood. May initially present with localized panniculitis which then becomes generalized. Often associated with other autoimmune diseases.
Mandibuloacral Dysplasia (MAD)-associated lipodystrophy	Autosomal recessive (LMNA)	0.33-1.8	Progeroid features, skeletal abnormalities (hypoplasia of mandibles and clavicles)

Table 3

Comparison of the phenotype of obesity with lipodystrophy.

	Obesity	Lipodystrophy
Total fat	High	Low
Leptin level	High	Low
Energy intake	High	High
Ectopic fat	Moderate	High
Insulin resistance	Moderate	Extreme
Insulin receptor expression	Regulated[1]	Regulated[1]

[1] Down-regulation of insulin receptor expression in hyperinsulinemic conditions (i.e. excess energy storage and leptin deficiency) and up-regulation in conditions of reduced insulin concentrations (i.e. fasting)[63].

Table 4

Phenotypic features of syndromic forms of insulin resistance versus the common metabolic syndrome.

	Insulin Resistance	Triglycerides	Adiponectin	Ectopic fat	PCOS features
Common Metabolic Syndrome	Yes ↑↑	Elevated ↑	Low ↓	Yes ↑↑	Yes ↑
Lipodystrophy	Yes ↑↑↑	Elevated ↑↑	Low ↓↓	Yes ↑↑↑	Yes ↑↑
Receptoropathies	Yes ↑↑↑↑	Low ↓	Elevated ↑↑	No	Yes ↑↑↑

PCOS, Polycystic Ovarian Syndrome