# 3 Prominent Insulin Resistance in Congenital Generalized Lipoatrophy

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**Keywords**
Lipodystrophy · Fatty liver · Insulin resistance · Leptin · Diabetes

## 3.1 Case Report

A 35-year-old female was admitted to the division of endocrinology and metabolism for generalized lipoatrophy and hyperglycemia. She was markedly deficient of adipose tissue since birth and developed diabetes and hypertension at the age of 20 years. She began receiving premixed biosynthetic human insulin with a ratio of 30% regular and 70% NPH (neutral protamine Hagedorn) insulin at the age of 27 years. The glycemic control remained poor despite the increase in her insulin dose to 60–80 units/day. Her hemoglobin A1c levels remained high, and they varied between 8 and 11%. Current admission revealed a female with 161 cm height, body weight 53.0 kg, body mass index (BMI) 20.4 kg/m$^2$, and systemic blood pressure of 146/86 mm Hg. She had muscular stature with generalized loss of subdermal fatty tissue. She also had umbilical hernia and acromegalic features with slight enlargement of her hands, feet, and mandible (Fig. 3.1a). She had difficulty in controlling her excessive appetite.

Her fasting plasma glucose was 222 mg/dl and HbA1c 8.4%. Serum c-peptide was 4.1 ng/mL and daily urinary excretion 85.2 μg/day, indicating her insulin secretion was not impaired. Her serum leptin level was extremely low, i.e., 0.8 ng/ml (normal range 1.7–14.5 ng/ml). Urinalysis revealed glucosuria and microalbuminuria of 261.3 mg/day. She had mild elevation of liver enzymes: aspartate transaminase (AST, 41 IU/l), alanine aminotransferase (ALT, 49 IU/l), alkaline phosphatase (ALP, 409 IU/l), and γ-glutamyl transferase (γ-GT, 53 IU/l) (Table 3.1). Computed tomography revealed absence of subdermal and visceral adipose tissues but notable fatty liver (Fig. 3.1b and c). She also had dyslipidemia with low HDL-cholesterol (35 mg/dl) and high triglyceride (257 mg/dl) levels. Euglycemic hyperinsulinemic clamp study targeting plasma glucose concentration of 95 mg/dl with insulin infusion rate of 1.25 mU/kg/min suggested a prominent insulin resistance since glucose infusion rate of 2.5 mg/kg/min (normal range 8.0–12.0 mg/kg/min) was required to maintain target glucose levels.

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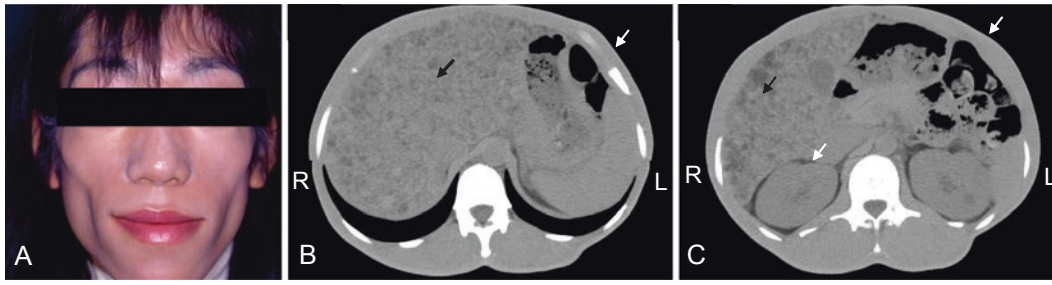


**Fig. 3.1** The presented case with congenital lipoatrophy. (**a**) Photograph of the patient. (**b**) and (**c**) Computed tomography of the abdomen. Prominent fatty liver is noted, and both subdermal and abdominal adipose tissues are absent. Black arrows indicate prominent fatty liver and white arrows absence of subdermal and retroperitoneal adipose tissues

Daily leptin replacement therapy was started with recombinant methionyl human leptin (metreleptin; 0.04 mg/kg BW), and after 1 month the dose was increased to 0.08 mg/kg BW. Subsequently, insulin therapy was discontinued, and metabolic profile, such as HbA1c and serum triglycerides, returned to within normal limits.

## 3.2 Diagnosis

This is a characteristic case of generalized lipoatrophy, diabetes with prominent insulin resistance, hypertension, dyslipidemia, and severe fatty liver. The lipodystrophic disorders are classified into two main categories, familial/congenital versus acquired lipodystrophy (Table 3.2). Both categories include total (generalized) and partial lipoatrophy. Genome sequencing analysis revealed that the patient had a mutation in the *BSCL2* (seipin lipid droplet biogenesis associated) gene, which confirmed the diagnosis (Table 3.3). Although the mutation of *BSCL2* gene was found later in life, the patient had generalized lipoatrophy since birth, and she was labeled with the diagnosis having congenital generalized lipodystrophy type 2 (Berardinelli-Seip syndrome).

## 3.3 Biochemical and Molecular Perspectives

*BSCL2* gene encodes multi-pass transmembrane protein seipin, which localizes to the endoplasmic reticulum. It is essential for adipocyte differentiation, lipid storage, and lipid droplet maintenance. Upon adipogenic differentiation, induced pluripotent stem (iPS) cells derived from patients with BSCL2 deficiency exhibit marked reduction of lipid droplet formation. In addition, seipin interacts with adipose differentiation-related protein (ADRP), and normal cytoplasmic punctate localization of ADRP has been reported to be lost in patient-derived iPS cells (Mori et al. 2016). Thus, the failure to form lipid droplets is linked to lipoatrophic phenotypes of such patients (Table 3.4).

The loss of adipose tissues in patients with Berardinelli-Seip syndrome can be linked to the reduction of secreted factors known as adipokines, such as adiponectin, leptin, and others. Leptin, a 167 amino acid adipokine, is mainly expressed in white adipose tissue (WAT) and plays an important role in energy homeostasis (Fig. 3.2). Leptin was initially discovered as a mutation in the leptin gene resulting in massive obesity and type 2 diabetes in human as well as in rodents. The adipose tissue mass positively correlates with serum concentration of leptin, and it

**Table 3.1** Laboratory data in present case

| Urinalysis and biochemistry | (Normal range in female) |
|---|---|
| Protein | (−) |
| Sugar | 4+ |
| pH | 5.5 |
| Ketone | (−) |
| Occult blood | (−) |
| Creatinine clearance | 83.6 mL/min/1.73m$^2$ (80–140) |
| Daily albumin excretion | 261.3 mg/day (−30) |
| **Peripheral blood cell count** | |
| White blood cells | 3400/μL (3500–9000) |
| Red blood cells | 370 × 10$^4$/μL (350–500) |
| Hemoglobin | 11.4 g/dL (12.0–16.0) |
| Platelets | 19.4 × 10$^4$/μL (15–35) |
| **Serum biochemistry** | |
| Total protein | 8.1 g/dL (6.5–8.0) |
| Albumin | 4.4 g/dL (4.0–5.0) |
| Aspartate transaminase | 41 IU/L (10–35) |
| Alanine aminotransferase | 49 IU/L (5–30) |
| Lactate dehydrogenase | 194 IU/L (120–220) |
| Alkaline phosphatase | 409 IU/L (100–350) |
| γ-glutamyl transferase | 53 IU/L (10–30) |
| Creatinine | 0.62 mg/dL (0.4–0.8) |
| Uric acid | 5.4 mg/dL (2.5–6.0) |
| Urea nitrogen | 13.2 mg/dL (8–20) |
| Sodium | 137 mmol/L (138–145) |
| Potassium | 4.5 mmol/L (3.6–4.8) |
| Chloride | 98 mmol/L (101–108) |
| Total cholesterol | 190 mg/dL (130–220) |
| Triglyceride | 226 mg/dL (30–150) |
| High-density lipoprotein-cholesterol | 38 mg/dL (40–100) |
| Low-density lipoprotein-cholesterol | 97 mg/dL (65–163) |
| **Glucose metabolism** | |
| Hemoglobin A1c | 8.4% (4.6–6.2) |
| Fasting plasma glucose | 222 mg/dL (80–110) |
| Serum C-peptide | 4.1 ng/mL (1.1–4.4) |
| Daily urinary C-peptide excretion | 95.2 μg/day (50–100) |
| Leptin | 0.8 ng/mL (1.7–14.5) |
| Immunoreactive insulin (IRI)* | 191.7μU/mL (1.7–10.4) |

*IRI was measured under daily injection of insulin

**Table 3.2** Classification of lipodystrophies (Huang-Doran et al. 2010)

| **Congenital lipodystrophy** |
|---|
| Congenital generalized lipoatrophy (CGL) |
| Familial partial lipoatrophy (FPLD) |
| **Acquired lipodystrophy** |
| Acquired generalized lipoatrophy |
| Autoimmune disorders-associated (juvenile dermatomyositis, SLE, autoimmune hemolytic anemia, autoimmune hepatitis, low C4 complement levels) |
| Acquired partial lipoatrophy |
| HIV-associated |
| C3 nephritic factor-associated |

**Table 3.3** Classification of congenital generalized and partial lipodystrophy and causal genes

| **Congenital generalized lipoatrophy (CGL)** | **Official gene symbol** |
|---|---|
| CGL type 1 (CGL1) | *AGPAT2* |
| CGL type 2 (CGL2) | *BSCL2* |
| CGL type 3 (CGL3) | *CAV1* |
| CGL type 4 (CGL4) | *PTRF* |
| **Familial partial lipodystrophy (FPLD)** | **Official gene symbol** |
| FPLD type 1 (Kobberling's syndrome) | Unknown |
| FPLD type 2 (Dunnigan's syndrome) | *LMNA* |
| FPLD type 3 | *PPARG* |
| FPLD type 4 | *AKT2* |
| FPLD type 5 | *PLIN1* |

**Table 3.4** Major clinical features of lipodystrophies (Brown et al. 2016)

| |
|---|
| Generalized or regional absence of body fat |
| Severe acanthosis nigricans |
| Prominent muscles and veins |
| Cushingoid, acromegaloid, and progeroid appearance |
| Diabetes mellitus with high insulin requirements |
| Severe hypertriglyceridemia |
| Nonalcoholic steatohepatitis in a nonobese individual |
| Early-onset cardiomyopathy |
| Polycystic ovarian syndrome (PCOS) |
| Renal dysfunction (proteinuria, diabetic nephropathy) |
| Significant hyperphagia |

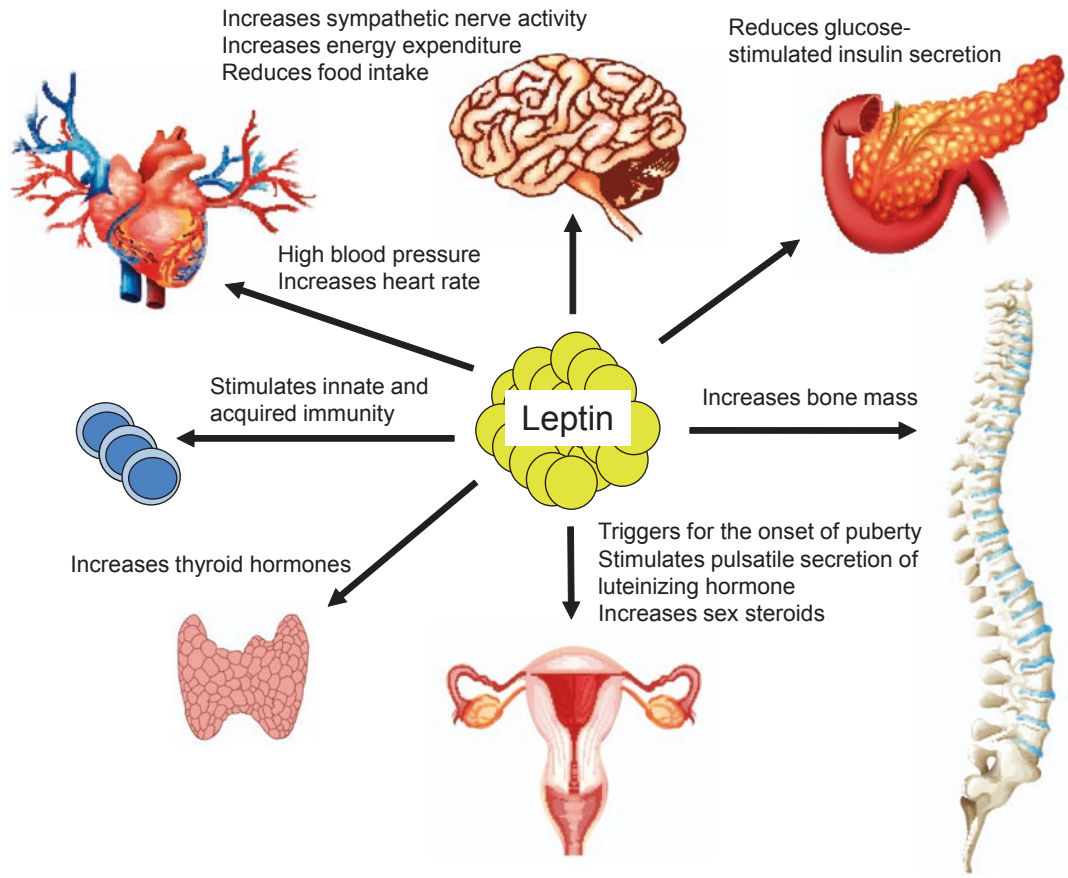


**Fig. 3.2** Diverse physiological actions of leptin

is a marker of acute changes in energy intake. Upon increased energy intake and subsequent increase in adipose tissue mass, leptin is secreted by the adipocytes (Fig. 3.3).

Once in blood circulation, it crosses the blood-brain barrier, and binds to leptin receptor in the hypothalamus, including supraoptic, paraventricular, periventricular, and arcuate nuclei and lateral hypothalamus, following which it activates Janus kinase (JAK)-signal transducer and activator of transcription 3 (STAT3) signal pathway. Specifically, leptin activates anorexigenic pro-opiomelanocortin (POMC) and cocaine- and amphetamine-regulated transcript (CART) neurons, while it suppresses orexigenic agouti-related peptide (AgRP) and neuropeptide Y (NPY) neurons. These series of events result in the inhibition of feeding behavior and increased energy expenditure to maintain whole-body adipose tissue mass (Fig. 3.4). Leptin also regulates hypothalamus-pituitary-endocrine organs axis, and low leptin levels are associated with reduced levels of gonadotropins, thyroid hormones, and growth hormone secretion in obese patients with congenital leptin deficiency(Farooqi et al. 1999). In such young patients, thyroid and luteinizing hormones (LH) with pulsatile secretion, sex steroid levels can be restored with the supplementation of leptin, and the rising leptin levels can be interpreted as triggers for the onset of normal puberty (Mantzoros et al. 1997) (Fig. 3.2).

In addition to central action, leptin also exerts various effects on peripheral organs, such as the adipose tissue, muscle, liver, pancreas, cardiovas-

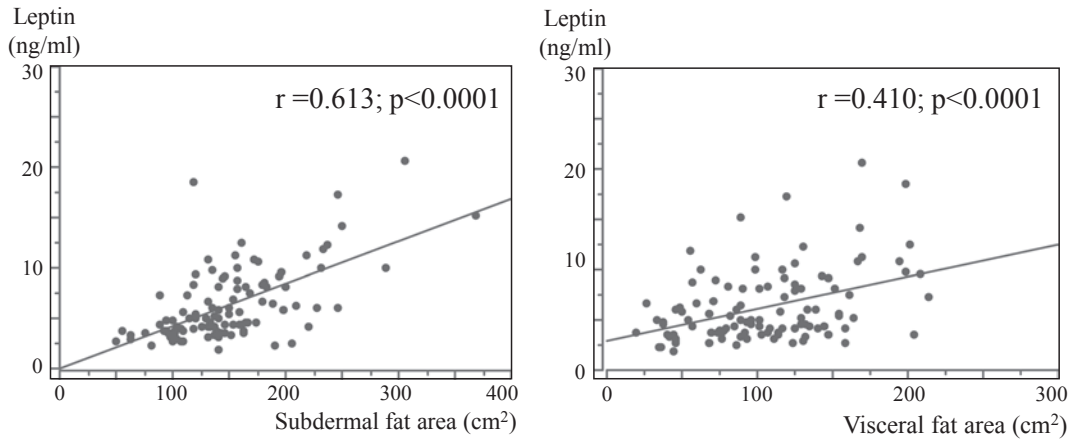


**Fig. 3.3** The correlation of serum leptin levels with subdermal and visceral adipose tissues in Japanese men (Kunitomi et al. 2002)

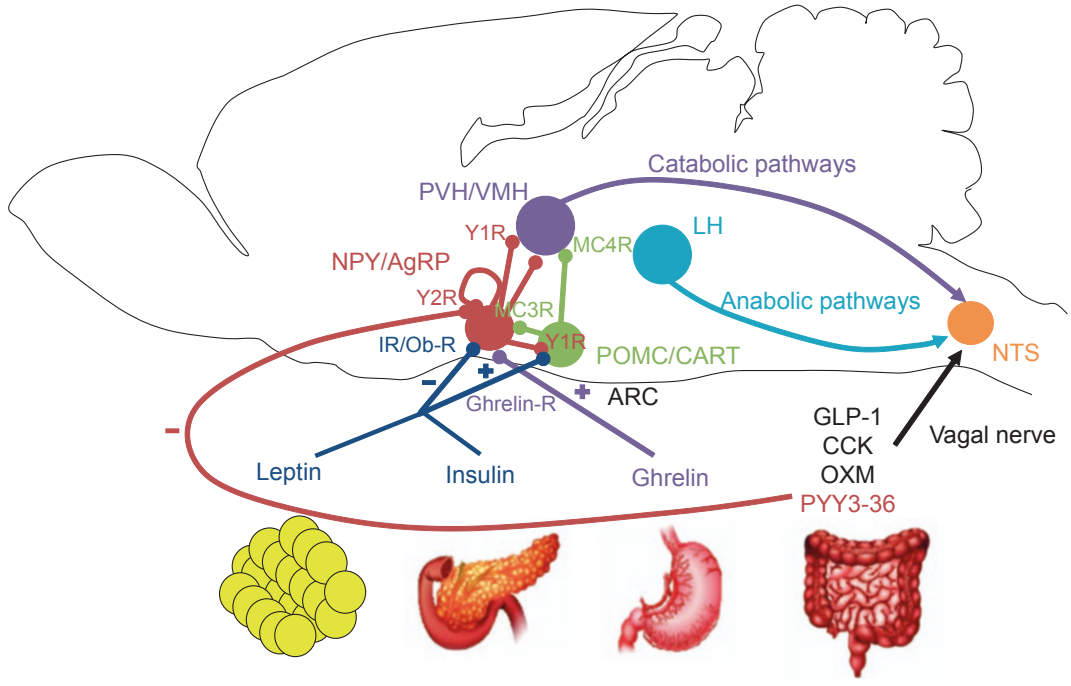


**Fig. 3.4** Peripheral and central control of appetite and satiety. *ARC* arcuate nucleus, *CCK* cholecystokinin, *GLP-1* glucagon-like peptide-1, *Ghrelin-R* ghrelin receptor, *IR* insulin receptor, *MC3R* melanocortin 3 receptor, *MC4R* melanopcortin 4 receptor, *NPY/AgRP* neuropeptide Y/agouti-related protein neurons, *NTS* nucleus of the solitary tract, *Ob-R* leptin receptor, *OXM* oxyntomodulin, *PVH/VMH* paraventricular hypothalamus/ventromedial hypothalamus, *PYY3-36* peptide YY3-36, *POMC/CART* proopiomelanocortin/cocaine- and amphetamine-regulated transcript, *Y1R* peptide YY Y1 receptor, *Y2R* peptide YY Y2 receptor

cular system, and bone. Leptin directly acts on brown (BAT) and WAT, increases glucose utilization, and upregulates rate of lipolysis, as demonstrated in Zucker *fa/fa* rats with loss of function in the mutated leptin gene (Siegrist-Kaiser et al. 1997). In leptin-deficient *ob/ob* mice, accumulation of triacylglycerol (TAG) in skeletal muscle contributes to insulin resistance, and it should be noted that normally leptin decreases glycogen synthesis and oleate incorporation into TAG and increased oleate oxidation (Muoio et al. 1999). Acute leptin infusion stimulates hepatic fatty acid oxidation and reduces TAG, and these metabolic processes are dependent of phosphoinositol-3-kinase (PI3K) activity (Huang et al. 2006). In addition, leptin treatment reverses hyperglycemia in animal models of poorly controlled type 1 diabetes by reducing hepatic gluconeogenesis (Perry et al. 2014). One of the important peripheral actions of leptin is inhibition of insulin biosynthesis and secretion by pancreatic β-cells. In turn, insulin stimulates leptin secretion from adipose tissue; and this hormonal negative feedback system, an adipo-insular axis, plays an important role in the maintenance of body weight and glucose metabolism. In fact, the disruption of leptin receptor in pancreatic β-cells in mice results in obesity, fasting hyperinsulinemia, impaired glucose-stimulated insulin release, and glucose intolerance without changes in food intake and satiety responses to leptin (Covey et al. 2006).

Despite marked obesity associated with components of metabolic syndrome, such as visceral obesity, insulin resistance, hyperglycemia, dyslipidemia in patients with leptin, or leptin receptor deficiency, they are not hypertensive or have increased sympathetic nerve system (SNS) activities. Interestingly, chronic injection of leptin into lean rodents results in gradual elevation of blood pressure, suggesting slow-acting mechanism, such as modest renal SNS activation to increase sodium reabsorption rather than massive systemic SNS activation associated with peripheral vasoconstriction (Foo et al. 2014). Also the consensus is that chronic administration may lead to "selective" resistance to appetite suppressing actions of leptin, whereas cardiovascular effects of leptin remain operative or even get enhanced in the control of blood pressure.

The generalized decrease in systemic adipose tissue (lipoatrophy) and localized loss of adipose mass is associated with hypoleptinemia. This is commonly categorized under lipodystrophic disorders, consisting of both familial/congenital as well acquired lipodystrophy (Table 3.2).

Although congenital lipodystrophic disorders are rare, they are more commonly associated with the patients with human immunodeficiency virus (HIV) and use of highly active antiretroviral therapy (HAART), and this is referred to as HIV-associated lipodystrophy. By the use of HAART, viremia in HIV patients is well-controlled, and they live longer; however, they acquire significant metabolic risks including development of lipodystrophy, hypoleptinemia, insulin resistance, and atherosclerosis (Tsoukas et al. 2015). These patients usually manifest with hyperinsulinemia, prominent insulin resistance, diabetes, hepatic steatosis, and dyslipidemia with notable elevation of TAG. In such a state, inadequate and reduced capacity for lipid accumulation in adipose tissue results in ectopic lipid deposition and lipotoxicity in various organs, e.g., liver, pancreas, and heart. These lipodystrophic patients suffer from pseudoathletic muscular hypertrophy, hypertrophic and dilated cardiomyopathy, acute pancreatitis, steatohepatitis, and liver cancers. Moreover, in obese patients, the adipocyte overload with lipid causes fatty acid efflux from adipose tissue and ectopic lipid deposition. The obese subjects usually demonstrate hyperleptinemia, and the leptin resistance causes prominent insulin resistance with increased food intake and reduced satiety response to leptin. Obese subjects also develop metabolic syndrome manifesting with prominent insulin resistance, hyperglycemia, hypertension, dyslipidemia, and fatty liver disease. Although the physique characteristics and serum concentrations of leptin are totally different in patients with lipodystrophy and obesity, they have similar metabolic defects and common target organ complications (Fig. 3.5).

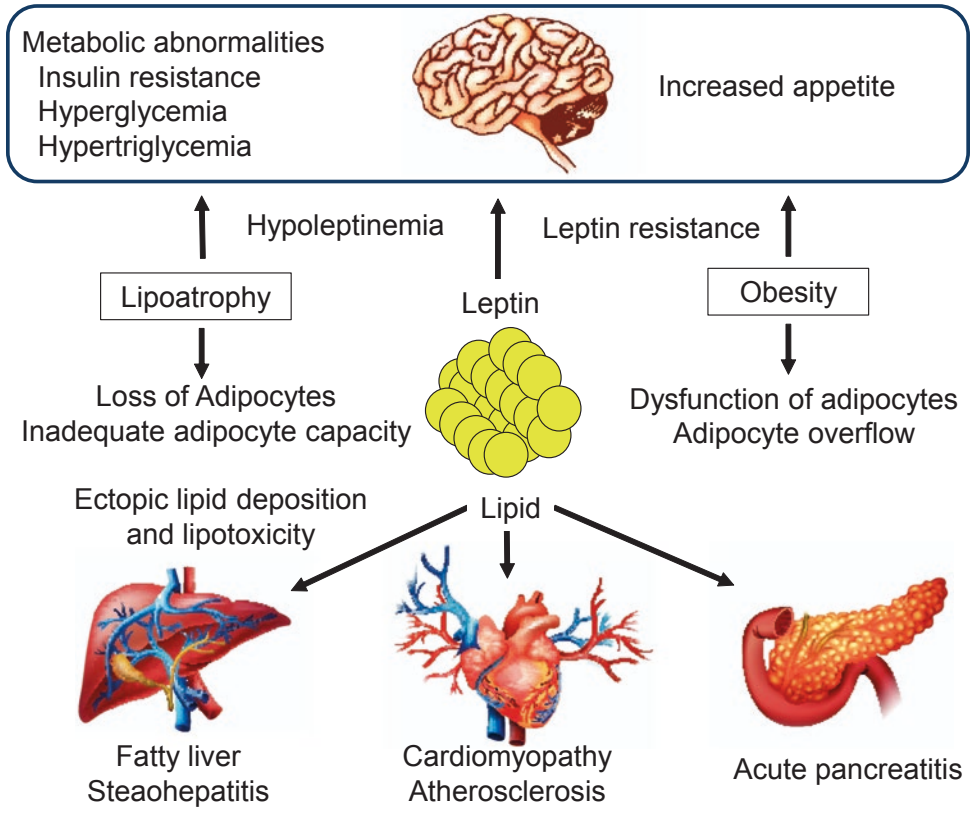


**Fig. 3.5** The analogies in the pathogenesis of lipoatrophy and obesity

## 3.4 Therapy

Severe lipodystrophy is associated with leptin deficiency, insulin resistance, hypertriglyceridemia, and hepatic steatosis; and leptin replacement therapy ameliorates these metabolic disturbances (Oral et al. 2002). Currently available therapy in humans is the administration of metreleptin. The US Food and Drug Administration (USFDA) and Pharmaceuticals and Medical Devices Agency (PMDA) in Japan have approved the use of metreleptin to treat complications of leptin deficiency in patients with congenital or acquired generalized lipodystrophy as a replacement therapy in addition to diet therapy. In certain patients undergoing replacement therapy develop anti-metreleptin antibodies with neutralizing activity and severe infection and begin to show signs indicative of the loss of metreleptin efficacy.

Due to the beneficial effects of leptin, the use of metreleptin has been also evaluated in other disease states, such as obesity, type 1 and 2 diabetes, HIV-associated lipodystrophy, and hypothalamic amenorrhea (HA). In general, metreleptin has not been shown to be effective in state of obesity without congenital leptin deficiency since the development of neutralizing anti-metreleptin antibodies has been reported in such patients. In obesity, at times there is prominent leptin resistance, and metreleptin effectiveness would be compromised, in such cases a combination of pramlintide/metreleptin has been evaluated in clinical trials (Ravussin et al. 2009). It is worth mentioning here that energy homeostasis and control of body weight involve complex communications between the central nervous system and peripheral neurohormonal signals from various tissues that integrate long-term adiposity signals of leptin (metreleptin) and short-term satiation signals of amylin (pramlintide). Thus, combined use of these polypeptide hormones would be warranted. Unfortunately, the combined treatment with pramlintide and

metreleptin although resulted in a significant weight loss, the development of anti-metreleptin antibodies precluded their use in patients with obesity.

Fundamental defect in type 1 diabetes is impaired insulin secretion by pancreatic β-cells due to autoimmune-mediated loss, and thus insulin replacement is regarded as the choice of therapy in such patients. However, the involvement of other hormones, such as glucagon and leptin, should be also taken into account in the treatment of diabetes. The absence of glucagon receptor prevents the elevation of blood glucose, fasting and non-fasting free fatty acid, and β-hydroxy butyrate levels in mouse model treated with a double dose of streptozotocin to maximize β-cell destruction (Lee et al. 2011). Leptin treatment also reverses hyperglycemia in rat models of poorly controlled type 1 diabetes by correcting hyperglycemia and hepatic gluconeogenesis (Perry et al. 2014). Reduced leptin levels increase hypothalamic pituitary adrenal (HPA) axis activity, elevate CRF, ACTH and corticosterone levels, and promote fasting hyperglycemia and diabetic ketoacidosis in rat models of poorly controlled type 1 diabetes, as a result, a markedly higher rate of lipolysis and hepatic gluconeogenesis would be anticipated (Fig. 3.6). In addition, leptin replacement has been shown to decrease central fat mass and improve insulin sensitivity, dyslipidemia, and glucose levels in lipodystrophy commonly associated with HIV (Tsoukas et al. 2015; Lee et al. 2011). In view of the above, it may be worth investigating thoroughly long-term

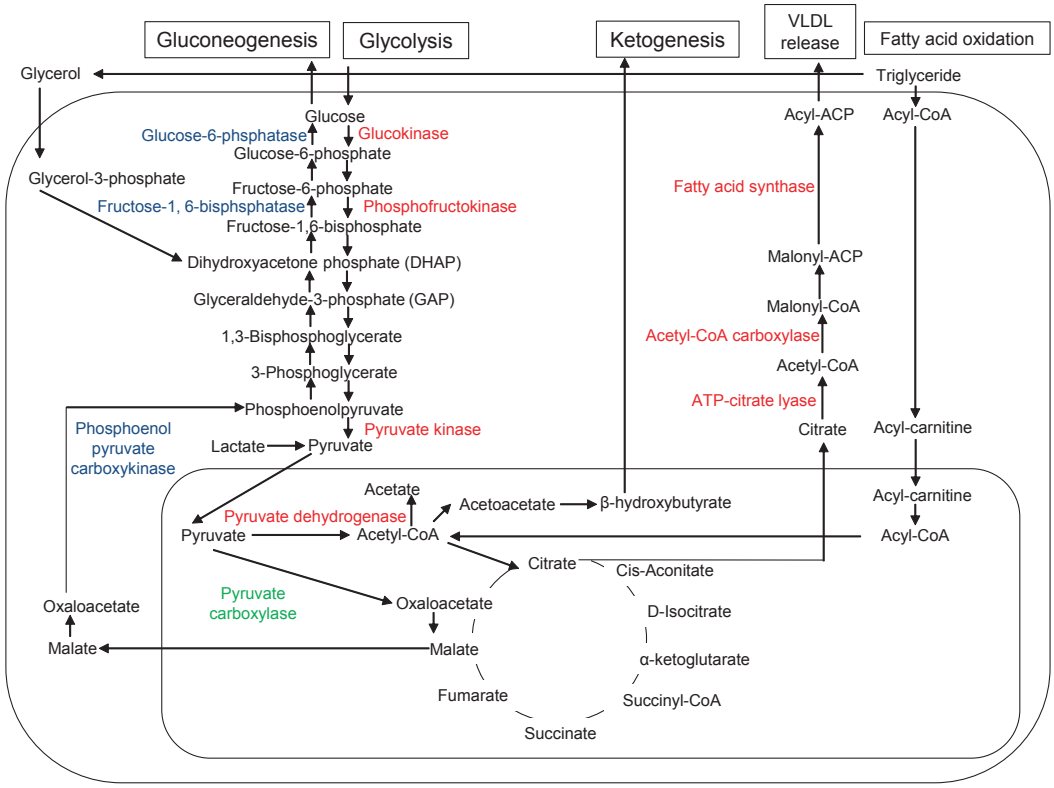


**Fig. 3.6** Lipid and glucose metabolic pathways in liver cells. Glycolytic and fatty acid synthetic enzymes are stimulated by insulin and inhibited by cortisol (red). The enzymes involved in gluconeogenesis is simulated by cortisol and inhibited by insulin (blue). The activity of pyruvate carboxylase is enhanced by acetyl-CoA and inhibited by insulin (green). In diabetic ketoacidosis, hypoleptinemia results in enhanced CRF/ACTH/corticosterone axis. It results in higher rate of lipolysis, conversion of glycerol to glucose, and conversion of pyruvate to glucose through greater hepatic acetyl-CoA allosteric activation of pyruvate carboxykinase flux

benefits of leptin replacement whether the administration of leptin protects the patients with HIV-associated lipodystrophy and shields them from the development of severe atherosclerosis and thus improves their life span.

Finally, it should be noted that young women with ample physical activity, reduced food intake, and too much stress, such as in athletes, are known to develop relative leptin deficiency and HA. In athletes, HA is often accompanied with eating disorders, infertility, and premature osteoporosis. The leptin replacement therapy usually restores the rhythmicity of menstrual cycles, and levels of estrogens, thyroid hormones, and IGF-1, and also increases bone formation (Foo et al. 2014).

**End-of-Chapter Questions**

1. Which symptoms does the leptin resistance provoke in the patients with obesity?
2. Which symptoms does hypoleptinemia induce in the patients with lipoatrophy?
3. Which symptoms does the congenital leptin deficiency and leptin receptor deficiency induce in human?
4. What are the differences in effectiveness of leptin administration in the patients with obesity, lipoatrophy, congenital leptin deficiency, and leptin receptor deficiency?

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