Recent advances in understanding lipodystrophy: a focus on lipodystrophy-associated cardiovascular disease and potential effects of leptin therapy on cardiovascular function

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Abstract

Lipodystrophy is a disease characterized by a partial or total absence of adipose tissue leading to severe metabolic derangements including marked insulin resistance, type 2 diabetes, hypertriglyceridemia, and steatohepatitis. Lipodystrophy is also a source of major cardiovascular disorders which, in addition to hepatic failure and infection, contribute to a significant reduction in life expectancy. Metreleptin, the synthetic analog of the adipocyte-derived hormone leptin and current therapy of choice for patients with lipodystrophy, successfully improves metabolic function. However, while leptin has been associated with hypertension, vascular diseases, and inflammation in the context of obesity, it remains unknown whether its daily administration could further impair cardiovascular function in patients with lipodystrophy. The goal of this short review is to describe the cardiovascular phenotype of patients with lipodystrophy, speculate on the etiology of the disorders, and discuss how the use of murine models of lipodystrophy could be beneficial to address the question of the contribution of leptin to lipodystrophy-associated cardiovascular disease.

Keywords

lipodystrophy, cardiovascular disease, metreleptin, cardiomyopathy, hypertension
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Introduction

Lipodystrophy is a group of clinically heterogeneous diseases characterized by either complete or partial absence of adipose tissue which may occur in conjunction with adipose mass redistribution and can be of either congenital or acquired origin. While inherited forms of generalized or partial lipodystrophies are exceedingly rare (1 in 10 million and 1 in 1 million, respectively) and mainly caused by autosomal recessive mutations of the AGPAT2, Berardinelli-Seip congenital lipodystrophy 2 (BSCL2), caveolin 1 (CAV1), PTRF genes or lamin A/C gene, acquired forms of lipodystrophy, on the other hand, have a relatively higher prevalence with an estimated number of 100,000 patients in the United States. Autoimmune disorders and medications including highly active antiretroviral therapy in HIV-infected patients are the leading causes of acquired generalized and partial lipodystrophy.

Regardless of the origin of the disease, patients with lipodystrophy share common metabolic abnormalities, which include marked insulin resistance, diabetes mellitus, and hypertriglyceridemia, the severity of which is typically related to the degree of fat loss. Metabolic derangements associated with lipodystrophy develop early in life and predispose patients to pancreatitis, non-alcoholic steatohepatitis (NASH), and hepatic failure, the latter being the first cause of morbidity and mortality and of substantial reduction in lifespan (of approximately 30 years) in patients with lipodystrophy. Although less studied and described, cardiovascular disorders including hypertrophic cardiomyopathy, hypertension, and atherosclerosis are also highly prevalent in lipodystrophic patients and additional major contributors to their shortened lifespan.

A key feature of lipodystrophy is a drastic reduction in the levels of adipocyte-derived hormones including leptin, which is a major regulator of appetite, insulin sensitivity, and liver function. Strong basic science and clinical evidence have demonstrated that daily supplementation with leptin in rodent models of lipodystrophy and patients with lipodystrophy restores appetite, glycemia, and hepatic and renal function. Based on these key findings, metreleptin, the recombinant human leptin analog, has been adopted as the therapeutic of choice for the treatment of lipodystrophy and approved by the US Food and Drug Administration (FDA) in February 2014 for the treatment of metabolic abnormalities in patients with congenital generalized and acquired lipodystrophy. However, leptin does more than targeting the metabolic system. Leptin is a pleiotropic hormone which controls numerous organ systems and has been positively associated with hypertrophic cardiomyopathy, hypertension, and vascular inflammation in the context of obesity. Whether restoring leptin levels in lipodystrophic patients with metreleptin represents a cardiovascular risk remains unclear. The goal of the present manuscript is to review the clinical and basic science literature to provide a current description of the cardiovascular diseases developed by lipodystrophy patients and rodent models of lipodystrophy and discuss the potential cardiovascular consequences of supplementing lipodystrophy patients chronically with leptin.

Cardiovascular diseases associated with lipodystrophy

Cardiomyopathy, demonstrated by echocardiography and ECG, is a frequent finding in patients with both congenital and acquired forms of lipodystrophy, who develop similar cardiac abnormalities. A majority of patients with lipodystrophy presents hypertrophic cardiomyopathy as early as 6 months of age, as reported in a young girl with congenital generalized lipodystrophy due to seipin (BSCL2) mutation. Minimal numbers of patients with lipodystrophy have features of dilated cardiomyopathy. Classically, it is believed that congenital lipodystrophy patients with underlying BSCL2 mutation have the highest prevalence of cardiomyopathy. Up to 80% of those affected have been reported to develop left ventricular hypertrophy with frequent abnormalities on ECGs resulting from long QT syndrome and a predisposition to tachyarrhythmias, including catecholaminergic polymorphic ventricular tachycardia and sudden cardiac death. Patients with underlying AGPAT mutation present a lower, but still high, prevalence (53%) of left ventricular hypertrophy. Lastly, patients with acquired generalized lipodystrophy have been reported to develop cardiac hypertrophy but of a significantly milder nature.

Cardiomyopathies and sudden cardiac arrest contribute to the high prevalence of death from cardiovascular causes and to the very early mortality of patients with lipodystrophy. Owing to the rarity of the disease and the paucity of patients, actual data on the cause of death in lipodystrophy patients remain scarce. Nevertheless, a recent study in 20 congenital lipodystrophy patients with BSCL2 mutation reported a mean age of death of 27 years old, with death from cardiovascular causes representing the third cause of death after hepatic failure and respiratory infection.

The underlying etiology of the cardiac abnormalities in lipodystrophy remain unclear. Severe insulin resistance and hyperlipidemia, which are characteristic of lipodystrophy patients, may provide the context for the development of hypertrophic cardiomyopathy. However, hypertrophic cardiomyopathy is more frequently seen in patients with BSCL2 mutation, who have overall milder metabolic abnormalities (including lower triglyceride levels and glycated hemoglobin) than in the AGPAT or acquired lipodystrophy groups. Hypertension, another major contributor to cardiomyopathy, affects between 30 and 50% of patients with lipodystrophy. However, whether patients with BSCL2 mutation who have the highest prevalence of cardiomyopathy are also more prone to hypertension remains unknown. One can hope that future clinical studies investigating the effects of metreleptin on cardiomyopathy will help address the question of the respective contribution of insulin resistance and hyperlipidemia, as well as hypertension, to lipodystrophy-associated cardiomyopathy. Indeed, metreleptin, the human recombinant leptin analog recently approved for the treatment of metabolic disorders associated with lipodystrophy, has proven to be efficacious at restoring insulin sensitivity and lipids levels but failed to restore blood pressure in patients with lipodystrophy. An improved cardiac function with metreleptin would support a role for
metabolic disorders in lipodystrophy-associated cardiomyopathy. Experimental studies in animal models of lipodystrophy represent an additional avenue for investigation of the underlying mechanisms.

Dyslipidemia and diabetes are leading causes of vascular disease and atherosclerosis. However, despite high prevalence of marked lipidemia and diabetes, only a few cases of atherosclerosis have been reported in lipodystrophy patients with either BSCL2 or AGPAT2 mutations. The relatively young age of the patients at the time of the study or death may explain the low prevalence for an age-related disease. In opposition to patients with other forms of lipodystrophy, patients with familial partial lipodystrophy (FPLD) and notably females suffering from the Dunnigan-type exhibit a high prevalence of coronary artery disease most likely caused by a very severe hypertriglyceridemia. Although meteletin treatment has proven to markedly reduce triglyceride levels in FPLD, it remains unknown whether it could reduce the incidence of atherosclerosis in these patients.

Together, these reports highlight the severity of the cardiovascular disorders developed by lipodystrophy patients and our lack of knowledge of their pathogenesis as well as stress our need for additional studies investigating their underlying mechanisms.

Table 1 summarizes the metabolic and cardiovascular alterations reported in patients with different forms of lipodystrophy.

**Cardiovascular disease in mouse models of lipodystrophy**

The rare aspect of the disease, its difficult diagnosis, and its consequent paucity in patients represent major limiting factors to the study of the etiology and pathological manifestations of lipodystrophy. Fortunately, several mouse models, which reproduce the metabolic and cardiovascular abnormalities observed in humans with lipodystrophy, have been developed and employed to better analyze the origins and consequences of this rare syndrome. The following section and Table 2 describe and discuss the phenotype of several of these models.

Constitutive deletion of BSCL2 and Cav1 or selective deletion of peroxisome proliferator activated receptor γ (PPARγ) and pro-renin receptor in adipocytes has been shown to reproduce the human congenital generalized lipodystrophy syndrome in mice. Each of these mouse models exhibit a near-complete absence of adipose tissue associated with impaired glucose tolerance and hyperlipidemia. Similarly, overexpression of the sterol regulatory element-binding protein-1c (SREBP-1c) and expression of the dominant negative A-ZIP/F-1 protein in adipose tissue reproduce well the human lipodystrophy phenotype in terms of fat mass and distribution as well as metabolic alterations. This close proximity between the metabolic phenotype of these mouse models and of human patients makes these murine models the ideal tool to investigate the etiology of cardiovascular disease in lipodystrophy.

The seipin-deficient (BSCL2−/−) mouse is the model that has been the most extensively studied for its cardiovascular phenotype. Several groups have observed that BSCL2−/− mice, just like lipodystrophy patients, exhibit cardiac hypertrophy very early in life, as early as postnatal day 10. Cardiac hypertrophy persists throughout adulthood and progresses to cardiomyopathy with aging. Results gathered with independent lines of BSCL2 knockout mice concur on the structural and hemodynamic alterations induced by lipodystrophy but diverge on the pathogenesis of the cardiac phenotype. Joubert et al. reported no intramyocardial lipid accumulation or lipotoxic hallmarks but detected increased myocardial glucose uptake and O-GlycNAcylated protein in BSCL2−/− hearts, in support of a cardiac glucose overload. Additional arguments in furtherance of an impaired cardiac glucose metabolism were provided by demonstrating that treatment with the hypoglycemic sodium glucose cotransporter 2 (SGLT2) inhibitor dapagliflozin prevented the development of hypertrophic cardiomyopathy in BSCL2−/− mice. Zhou et al.,

| Human disease | Genetic changes | Function of gene | Metabolic Phenotype | CV phenotype | Ref |
|---------------|-----------------|------------------|---------------------|-------------|-----|
| Berardinelli-Seip congenital lipodystrophy | Mutation in AGPAT2 and BSCL2 | Important in lipid droplet formation and adipocyte maturation | Enlarged and fatty liver, drastic reduction in fat mass, hyperinsulinemia, hyperglycemia, and hypertriglyceridemia | Cardiac hypertrophy, LV dysfunction, calcific aortic valve, and hypertension | 37,38,43 |
| Mutant PPARγ | Heterozygous mutations in the ligand-binding domain of PPARγ | Adipogenesis and adipocyte differentiation | Elevated glucose and insulin | Hypertension | 57,58 |
| Dunnigan type (FPLD2) | Mutations in LMNA encoding nuclear lamin A/C | Inhibits adipocyte differentiation | Insulin resistance | Hypertension and moderate LV dysfunction and dilation | 38,59,60 |

AGPAT2, 1-acyl-sn-glycerol 3-phosphate O-acyltransferase 2; Bsci2, Berardinelli-Seip congenital lipodystrophy 2; C/EBP, CCAAT-enhancer-binding proteins; CV, cardiovascular; FPLD2, familial partial lipodystrophy type 2; LV, left ventricle; PPARγ, peroxisome proliferator-activated receptor gamma; SREBP-1c, sterol regulatory element-binding protein 1.
Table 2. Mouse models of lipodystrophy and their characteristics.

| Mouse model | Genetic manipulation | Function of gene | Metabolic phenotype | CV phenotype | Ref |
|-------------|----------------------|------------------|---------------------|--------------|-----|
| Caveolin 1  | Global deficiency    | Role in lipid droplet formation by regulating lipids and phospholipid translocation across the plasma | Elevated TG and reduced leptin plasma levels | Vascular dysfunction, right ventricular hypertrophy, cardiomyopathy, and protected from atherosclerosis | 49,62–64 |
| AGPAT2      | Global deficiency    | Catalyzes the acylation of lysophosphatidic acid to phosphatidic acid | Hyperglycemia, elevated HbA1c, hyperinsulinemia, enlarged livers, and very low adiponectin and leptin levels | Not described | 65–67 |
| Bscl2/Seipin | Global               | Important for lipid droplet formation and adipocyte maturation | Enlarged and fatty liver, drastic reduction in fat mass, plasma leptin, and adiponectin levels, hyperinsulinemia, and hyperglycermia | Cardiac hypertrophy, cardiac dysfunction, and endothelial dysfunction | 45,48,56,68 |
| Bscl2/Seipin | Adipocyte-specific deficiency | Important for lipid droplet formation and adipocyte maturation | Enlarged and fatty liver, drastic reduction in fat mass, plasma leptin, and adiponectin levels, hyperinsulinemia, and hyperglycermia | Not described | 48 |
| PPARγ       | Adipocyte-specific deficiency | Adipogenesis and adipocyte differentiation | Enlarged and fatty liver, reduced leptin, diabetes, and elevated TG | Not described | 50,51 |
| Pro-renin receptor | Adipocyte-specific deficiency | Receptor for pro-renin or renin | Hyperinsulinemia, enlarged liver and pancreas, and reduced leptin plasma levels | Hypertension | 52,69 |
| SREBP-1c    | Adipocyte-specific overexpression | Lipid biosynthesis in animal cells | Hyperinsulinemia, hyperglycermia, insulin resistance, fatty liver, and reduced leptin | Not described | 47,53 |
| A-ZIP/F-1   | Adipocyte-specific deficiency | ZIP/F prevents the DNA binding of B-ZIP transcription factors of both the C/EBP and Jun families | Hyperinsulinemia, hyperglycermia, elevated TG, and reduced leptin plasma levels | Vascular dysfunction and remodeling and hypertension | 54,70,71 |

AGPAT2, 1-acyl-sn-glycerol 3-phosphate O-acyltransferase 2; Bscl2, Berardinelli-Seipin congenital lipodystrophy 2; C/EBP, CCAAT-enhancer-binding proteins; CV, cardiovascular; PPARγ, peroxisome proliferator-activated receptor gamma; SREBP-1c, Sterol regulatory element-binding protein 1; TG, triglycerides.

on the other hand, identified an important link between hyperinsulinemia and organomegaly in lipodystrophic mice. They showed that activation of prohypertrophic insulin-like growth factor 1 receptor (IGF1R)-mediated PI3K/AKT signaling contributes to cardiac hypertrophy in BSCL2–/– mice. They also identified a unique pattern of cardiac lipid remodeling with reduced cardiac steatosis associated with adipose triglyceride lipase (ATGL) overexpression in hearts of BSCL2–/– mice and showed that ATGL haploinsufficiency could reverse lipodystrophy, insulin resistance, and cardiac derangements. While these two studies depart on the underlying pathological mechanisms of hypertrophic cardiomyopathy in BSCL2–/– mice, they strongly support a role for
metabolic alterations. Interestingly, using the exact same mouse as the mouse employed by Chen et al.\textsuperscript{44} and Zhou et al.\textsuperscript{45}, our group recently reported that lipodystrophy impairs aortic endothelium-dependent relaxation by mechanisms independent of metabolic function. Indeed, we showed that restoration of glycemia via SGLT2 inhibition failed to restore endothelial function. However, we demonstrated that the absence of adipose tissue characteristic of lipodystrophy induced a reduction in systemic leptin levels which diminished endothelial leptin signaling and caused endothelial dysfunction via an overproduction of reactive oxygen species by endothelial NADPH oxidase 1 (Nox1).\textsuperscript{46} Together, these observations further highlight the complexity of the disease and suggest that metabolic alterations are not the only cause of cardiovascular disease in lipodystrophy.

The Cav1\textsuperscript{−/−} mouse is another model that has been used to study lipodystrophy and also present cardiomyopathy.\textsuperscript{47,62-64,72} Differently from BSCL2\textsuperscript{−/−} mice, Cav1\textsuperscript{−/−} mice exhibit concentric left ventricular hypertrophy and dilated right ventricular hypertrophy. The discrepancy in the cardiac phenotype between BSCL2\textsuperscript{−/−} and Cav1\textsuperscript{−/−} might find its origin in the etiology of the cardiomyopathy. Indeed, as described above, metabolic disorders, notably insulin resistance and hyperglycemia, appear as the primary causes of cardiomyopathy in BSCL2\textsuperscript{−/−} mice. In opposition, in Cav1\textsuperscript{−/−} mice, cardiomyopathy was shown to be secondary to Cav1 deletion and pulmonary hypertension. Indeed, selective restoration of Cav1 expression in endothelial cells completely rescued pulmonary hypertension and cardiac hypertrophy in Cav1\textsuperscript{−/−} mice.\textsuperscript{71} Remarkably, Cav1\textsuperscript{−/−} mice are protected from atherosclerosis, again through mechanisms independent of lipodystrophy likely involving reduction in LDL infiltration into the artery wall, increased nitric oxide production, and reduction in the expression of leukocyte adhesion molecules.\textsuperscript{71} Therefore, the Cav1\textsuperscript{−/−} mouse may be less relevant to the study of lipodystrophy and its cardiovascular consequences.

A key feature of lipodystrophy is dyslipidemia, notably hyperlipidemia which, added to insulin resistance and diabetes, places patients with lipodystrophy at a high risk for atherosclerotic cardiovascular disease.\textsuperscript{71-79} To investigate whether lipodystrophy predisposes to atherosclerosis, Wang \textit{et al.}\textsuperscript{86} crossed BSCL2\textsuperscript{−/−} with low-density lipoprotein receptor (LDLr\textsuperscript{−/−}) knockout mice, a mouse model of atherosclerosis. As observed in lipodystrophic patients,\textsuperscript{30} LDLr\textsuperscript{−/−} BSCL2\textsuperscript{−/−} mice present with accelerated atherosclerosis, as reflected by spontaneous plaque formation on chow diet and exacerbation of atherosclerotic lesions on atherogenic diet.\textsuperscript{84} The absence of adipocytes, which decreases the potential for adipose cholesterol clearance, most likely explains the extremely high rise in plasma cholesterol levels in LDLr\textsuperscript{−/−} BSCL2\textsuperscript{−/−} mice which itself predisposed lipodystrophic mice to atherosclerosis.\textsuperscript{84}

Lastly, mouse models of lipodystrophy, as do patients, present with hypertension.\textsuperscript{33,48} Experiments conducted in transgenic A-ZIP/F-1 mice\textsuperscript{70,81} and adipose tissue pro-renin receptor-deficient mice\textsuperscript{52} revealed elevated systolic blood pressure associated with hyperactivation of the renin angiotensin system (RAS). Angiotensin-converting enzyme inhibition\textsuperscript{91} and angiotensin type 1 receptor blockade\textsuperscript{92} restored blood pressure in these two mouse models of lipodystrophy, which further supports the contribution of RAS to the development of hypertension in mouse models of lipodystrophy and presents RAS blockade as a potential avenue for the treatment of cardiovascular disease associated with lipodystrophy. However, whether RAS overactivation is consecutive to metabolic alterations remains to be determined.

**Metreleptin and lipodystrophy-associated cardiovascular disease**

Following many successful trials, the FDA has approved leptin (metreleptin) for the treatment of non-HIV-related forms of generalized lipodystrophy. Leptin replacement therapy with metreleptin has, in many cases, reversed the metabolic complications, with improvements in glucose-insulin-lipid homeostasis and regression of fatty liver disease.\textsuperscript{71,83,87-92,97-99} An aspect of the treatment that remains ill-defined is whether metreleptin improves or alters cardiovascular function in lipodystrophic patients. Compelling basic science and clinical evidence indicate that excess leptin elevates blood pressure and impairs vascular function via sympathetic-activation in males\textsuperscript{82-86} and aldosterone production in females.\textsuperscript{82,87,88} Therefore, concerns have been raised regarding the potential deleterious cardiovascular consequences of daily leptin injections. Recent results by Brown \textit{et al.} partially dissipated these concerns by reporting that metreleptin did not elevate blood pressure in a relatively large population of lipodystrophic patients (107 patients).\textsuperscript{30} Based on their results, the authors concluded that there was a lack of contribution of leptin to the development of hypertension and a lack of translatability of the results obtained in murine models. However, the significant improvements in glycemia, insulin resistance, and liver and renal function associated with metreleptin treatment\textsuperscript{85} were not considered by the authors to reach their conclusions. Indeed, insulin resistance has been presented as a major risk factor for hypertension.\textsuperscript{90,96} Therefore, the significant improvement in the metabolic profile of the lipodystrophy patients on metreleptin most certainly compensated for the indisputable effects of leptin on sympathetic tone.\textsuperscript{97} This may explain the lack of significant decreases in blood pressure in lipodystrophy patients on metreleptin. In addition, besides increasing sympathetic activity, leptin exerts vascular actions which could provide additional explanations for the lack of increase in blood pressure. Early work by the group of Lembo \textit{et al.}, and supported by others, demonstrated that leptin not only relaxes blood vessels via NO-dependent mechanisms\textsuperscript{92,93} but also controls vascular integrity by protecting vessels from neointima formation, excess endothelin 1 production, and increasing PPARy activity.\textsuperscript{98} Furthermore, recent results by our group show that leptin replacement therapy restores endothelium-dependent relaxation via direct activation of endothelial leptin receptor and reduction in Nox1-derived ROS.
production, likely via PPARγ-dependent mechanisms, in BSCL2−/− mice. Taken together, these results further support the direct vascular effects of leptin and indicate that metreleptin treatment should improve vascular function in lipodystrophy patients.

Other potential concerns are the chronic effects of metreleptin on cardiac function and remodeling. Indeed, while compelling in vitro studies have shown that leptin promotes human and rodent cardiomyocyte hyperplasia, several clinical studies have established a positive correlation between leptin and left ventricular hypertrophy after adjustment for body mass index and present leptin as an independent predictor of incident heart failure. Conversely, elegant rescue experiments involving either selective restoration of leptin receptor expression in cardiomyocytes of leptin receptor-deficient mice (db/db) or restoration of leptin levels in leptin-deficient (ob/ob) mice report a decreased heart mass and reduction in left ventricular wall thickness in response to leptin, supportive of the cardiac protective effects of leptin. In addition, selective cardiac leptin receptor deficiency resulted in transient left ventricular dysfunction and dramatic reduction in ejection fraction, while cardiac-specific overexpression of leptin receptors normalized cardiac triglyceride levels and diastolic function in db/db97. All together, these data derived from murine models support a beneficial role for leptin in cardiac function and metabolism (protection from lipotoxicity) but drastically contrast with the clinical studies. This further raises the question of the potential contribution of leptin deficiency to the cardiac disorders associated with lipodystrophy and of the effects of daily metreleptin injections on the severely impaired heart function of lipodystrophic patients. Additional studies are warranted to address these concerns.

Lastly, although not tested yet, one can reasonably speculate that metreleptin exerts protective effects against atherosclerosis. While insulin resistance, diabetes, and, more specifically, hyperlipidemia are leading risk factors for atherosclerosis, compelling evidence from relatively large (66 patients) studies have demonstrated that long-term treatment with metreleptin resulted in sustained improvements in hypertriglyceridemia, glycemic control, and liver volume which led to discontinuation of insulin, oral anti-diabetics, and lipid-lowering medications in more than 25% of patients on metreleptin98. Therefore, one can soundly anticipate that metreleptin will significantly reduce the drug’s efficacy or even inhibit endogenous leptin activity99, have been shown to develop in most patients within 4–6 months but to decrease with continuous therapy. In addition, few patients under metreleptin treatment have been shown to develop T-cell lymphoma. However, whether metreleptin is truly a contributor requires further investigation, as patients with lipodystrophy appear to be at a higher risk for lymphoma than the general population, likely because of underlying autoimmunity102. Therefore, metreleptin-associated side effects may still deserve some attention.

Conclusion
In summary, while the current literature on lipodystrophy focuses mostly on the metabolic disorders associated with the syndrome, cardiovascular diseases, notably hypertension and cardiomyopathy (Figure 1), also represent a major health concern in patients with lipodystrophy and contribute to their very early mortality. Here, we speculated that the metreleptin regimen provided to lipodystrophy patients may improve cardiovascular function through its beneficial effects on glycemia, lipidemia, and liver function. We also stressed that metreleptin may affect cardiac and vascular function through direct control of cardiomyocyte and endothelial cell function and highlighted the need for studies investigating whether metreleptin improves or impairs the function of these two types of cells. We presented several mouse models of lipodystrophy which reproduce well the metabolic and cardiovascular phenotype of patients with lipodystrophy and represent the perfect avenue to investigate the direct effects of leptin on the cardiovascular system and dissipate any potential harmful effect.
Figure 1. Potential Mechanisms leading to cardiovascular disease in lipodystrophy. Lipodystrophy is associated with a drastic reduction in adiposity and leptin plasma levels, which lead to hyperglycemia, lipotoxicity, and decreased cellular leptin signaling. These changes have been associated with non-alcoholic fatty liver disease (NAFLD), endothelial dysfunction, hypertension, and cardiac diseases.

References

1. Fiorenza CG, Chou SH, Mantzoros CS: Lipodystrophy: pathophysiology and advances in treatment. Nat Rev Endocrinol. 2011; 7(3): 137–50. PubMed Abstract | Publisher Full Text | Free Full Text
2. Yupanqui-Lozno H, Bastarrachea RA, Yupanqui-Velazco ME, et al.: Congenital Leptin Deficiency and Leptin Gene Missense Mutation Found in Two Colombian Sisters with Severe Obesity. Genes (Basel). 2019; 10(5): 342. PubMed Abstract | Publisher Full Text | Free Full Text
3. Metreleptin (Myalept): a leptin analog for generalized lipodystrophy. Med Lett Drugs Ther. 2015; 57(1460): 13–4. PubMed Abstract
4. Diker-Cohen T, Cochran E, Gorden P, et al.: Partial and generalized lipodystrophy: comparison of baseline characteristics and response to metreleptin. J Clin Endocrinol Metab. 2015; 100(5): 1802–10. PubMed Abstract | Publisher Full Text | Free Full Text
5. Garg A: Clinical review#: Lipodystrophies: genetic and acquired body fat disorders. J Clin Endocrinol Metab. 2011; 96(11): 3313–25. PubMed Abstract | Publisher Full Text
6. Hegele RA, Joy TR, Al-Attar SA, et al.: Thematic review series: Adipocyte Biology. Lipodystrophies: windows on adipose biology and metabolism. J Lipid Res. 2007; 48(7): 1433–44. PubMed Abstract | Publisher Full Text
7. Oral EA, Simha V, Ruiz E, et al.: Leptin-replacement therapy for lipodystrophy. N Engl J Med. 2002; 346(8): 570–8. PubMed Abstract | Publisher Full Text
8. Patni N, Garg A: Congenital generalized lipodystrophies–new insights into metabolic dysfunction. Nat Rev Endocrinol. 2015; 11(9): 522–34. PubMed Abstract | Publisher Full Text
9. Magré J, Delépine M, Khallouf E, et al.: Identification of the gene altered in Berardinelli-Seip congenital lipodystrophy on chromosome 11q13. Nat Genet. 2001; 28(4): 365–70. PubMed Abstract | Publisher Full Text
10. Kim CA, Delépine M, Boustet E, et al.: Association of a homozygous nonsense caveolin-1 mutation with Berardinelli-Seip congenital lipodystrophy. J Clin Endocrinol Metab. 2008; 93(4): 1129–34. PubMed Abstract | Publisher Full Text | F1000 Recommendation
11. Hayashi YK, Matsuda C, Ogawa M, et al.: Human PTRF mutations cause secondary deficiency of caveolins resulting in muscular dystrophy with generalized lipodystrophy. J Clin Invest. 2009; 119(9): 2623–33. PubMed Abstract | Publisher Full Text | F1000 Recommendation
12. Agarwal AK, Arioglu E, De Almeida S, et al.: AGPAT2 is mutated in congenital generalized lipodystrophy linked to chromosome 9q34. Nat Genet. 2002; 31(1): 21–3. PubMed Abstract | Publisher Full Text
13. Genschel J, Schmidt HH: Mutations in the LMNA gene encoding lamin A/C. Hum Mutat. 2000; 16(6): 451–9. PubMed Abstract | Publisher Full Text
14. Chan JI, Lutz K, Cochran E, et al.: Clinical effects of long-term metreleptin treatment in patients with lipodystrophy. Endocr Pract. 2011; 17(6): 922–32. PubMed Abstract | Publisher Full Text | Free Full Text
15. Goetzman ES, Tian L, Nagy TR, et al.: HIV protease inhibitor ritonavir induces lipoatrophy in male mice. AIDS Res Hum Retroviruses. 2003; 19(12): 1141–50. PubMed Abstract | Publisher Full Text
16. Machado MV, Cortez-Pinto H: Leptin in the treatment of lipodystrophy-associated nonalcoholic fatty liver disease: are we there already? Expert Rev Gastroenterol Hepatol. 2013; 7(6): 513–5. PubMed Abstract | Publisher Full Text
Metreleptin Treatment in Patients with Non-HIV Associated Lipodystrophy. Free Full Text | F1000 Recommendation
Brown RJ, Oral EA, Cochran E, et al.
Leptin-replacement therapy in lipodystrophy. J Clin Endocrinol Metab. 2007; 92(2): 532–41.
Published Abstract | Publisher Full Text
Edihara K, Kusakabe T, Hirata M, et al. Efficacy and safety of leptin-replacement therapy and possible mechanisms of leptin actions in patients with generalized lipodystrophy. J Clin Endocrinol Metab. 2009; 94(2): 252–41.
Published Abstract | Publisher Full Text
Munyappa R, Brown RJ, Mari A, et al. Effects of leptin replacement therapy on pancreatic β-cell function in patients with lipodystrophy. Diabetes Care. 2014; 37(4): 1101–7.
Published Abstract | Publisher Full Text | Free Full Text
Lima JG, Nobrega LHC, Lima NN, et al. Causes of death in patients with Berardinelli-Seip congenital generalized lipodystrophy. PLoS One. 2013; 18(6): e019902.
Published Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation
McGuire MJ, Ishii M. Leptin Dysfunction and Alzheimer’s Disease: Evidence from Cellular, Animal, and Human Studies. Cell Mol Neurobiol. 2016; 36(2): 203–17.
Published Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation
Pociol A, Morgan K, Buettner C, et al. Central leptin acutely reverses diet-induced hepatic insulin resistance. Diabetes. 2005; 54(11): 3182–9.
Published Abstract | Publisher Full Text
Haque MS, Minokoshi Y, Harati M, et al. Role of the sympathetic nervous system and insulin in enhancing glucose uptake in peripheral tissues after intrahypothalamic injection of leptin in rats. Diabetes. 1999; 48(9): 1706–12.
Published Abstract | Publisher Full Text
Minokoshi Y, Haque MS, Shizuma T. Microinjection of leptin into the ventromedial hypothalamic nucleus increases glucose uptake in peripheral tissues in rats. Diabetes. 1999; 48(2): 287–91.
Published Abstract | Publisher Full Text
Toda C, Shizuki T, Lee S, et al. Distinct effects of leptin and a melanocortin receptor agonist injected into medial hypothalamic nuclei on glucose uptake in peripheral tissues. Diabetes. 2009; 58(12): 2757–65.
Published Abstract | Publisher Full Text | Free Full Text
Brown RJ, Meachen CA, Cochran E, et al. Effects of Metreleptin in Pediatric Patients With Lipodystrophy. J Clin Endocrinol Metab. 2017; 102(5): 1511–1519.
Published Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation
Brown RJ, Valencia A, Starzel M, et al. Metreleptin-mediated improvements in insulin sensitivity are independent of food intake in humans with lipodystrophy. J Clin Invest. 2018; 128(8): 3504–3516.
Published Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation
Inui A. Leptin-replacement therapy in lipodystrophy. N Engl J Med. 2002; 346(25): 2009; author reply 2009–10.
Published Abstract | Publisher Full Text
Maurais-Janvis F. Leptin-replacement therapy in lipodystrophy. N Engl J Med. 2002; 346(25): 2009; author reply 2009–10.
Published Abstract | Publisher Full Text
Mulligan K, Khatami N, Schwartz JM, et al. The effects of recombinant human leptin on visceral fat, dyslipidemia, and insulin resistance in patients with human immunodeficiency virus-associated lipodystrophy and hypopituitarism. J Clin Endocrinol Metab. 2009; 94(4): 1137–44.
Published Abstract | Publisher Full Text | Free Full Text
Wolford J, Sadeghi-Nejad A, Senior B. Leptin-replacement therapy in lipodystrophy. N Engl J Med. 2002; 346(25): 2009; author reply 2009–10.
Published Abstract | Publisher Full Text
FDAs Myeplet FDA USA FOOD & DRUG, 2014, 2019.
Hall JD, de Carmona JM, da Silva AA, et al. Obesity-induced hypertension: interaction of neurohumoral and renal mechanisms. Circ Res. 2015; 116(6): 991–1006.
Published Abstract | Publisher Full Text | Free Full Text
Faulkner JL, Belin de Chantemelle EJ. Sex Differences in Mechanisms of Hypertension Associated With Obesity. Hypertension. 2018; 71(1): 15–21.
Published Abstract | Publisher Full Text | F1000 Recommendation
Bhaya S, Siv JM, Joubllet GJ, et al. Cardiomyopathy in congenital complete lipodystrophy. Clin Genet. 2002; 61(4): 283–7.
Published Abstract | Publisher Full Text
Luppa BC, Sachdev V, Lungu AO, et al. Cardiomyopathy in congenital and acquired generalized lipodystrophy: a clinical assessment. Medicine (Baltimore). 2010; 89(4): 245–50.
Published Abstract | Publisher Full Text | Free Full Text
Sanon VP, Handelman Y, Pham SV, et al. Cardiac Manifestations of Congenital Generalized Lipodystrophy. Clin Diabetes. 2016; 34(1): 181–186.
Published Abstract | Publisher Full Text | Free Full Text
Russi M, Patni N, Garg A. Lipodystrophies, dyslipidaemias and atherosclerotic cardiovascular disease. Pathology. 2019; 51(2): 202–212.
Published Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation
Prieur X, Le May C, Magré J, et al. Congenital lipodystrophies and dyslipidaemias. Curr Atheroscler Rep. 2014; 16(9): 437.
Published Abstract | Publisher Full Text | Free Full Text
Brown RJ, Meachen CA, Gordon P. Leptin Does Not Mediate Hypertension Associated With Human Obesity. Cell. 2015; 162(3): 465–66.
Published Abstract | Publisher Full Text
Rêgo AO, Mesquita ET, Faria CA, et al. Cardiometabolic abnormalities in patients with Berardinelli-Seip syndrome. An Bras Dermatol. 2010; 94(1): 109–18.
Published Abstract | Publisher Full Text | Free Full Text
Rochford Jr. Mouse models of lipodystrophy and their significance in understanding fat regulation, Curr Top Dev Biol. 2014; 109: 53–96.
Published Abstract | Publisher Full Text | Free Full Text
Chen W, Chang B, Sahar P, et al. Berardinelli-Seip congenital generalized lipodystrophy (BS2eip) in a cell-autonomous regulator of lipolysis essential for adipocyte differentiation. Mol Cell Biol. 2012; 32(6): 1099–111.
Published Abstract | Publisher Full Text | Free Full Text
Asterholm IW, Halberg N, Scherer PE. Mouse Models of Lipodystrophy: Key reagents for the understanding of the metabolic syndrome. Drug Discov Today Dis Malas. 2007; 4(1): 17–24.
Published Abstract | Publisher Full Text | Free Full Text
Leptin-replacement therapy in lipodystrophy. J Clin Endocrinol Metab. 2007; 92(2): 532–41.
Published Abstract | Publisher Full Text
Drab M, Verdeck M, Elger M, et al. Loss of caveolae, vascular dysfunction,
and pulmonary defects in caveolin-1 gene-disrupted mice. Science. 2001; 293(5539): 2449–52. PubMed Abstract | Publisher Full Text | F1000 Recommendation

63. Razani B, Engelman JA, Wang XB, et al.: Caveolin-1 null mice are viable but show evidence of hyperproliferative and vascular abnormalities. J Biol Chem. 2001; 276(41): 38212–38. PubMed Abstract | Publisher Full Text | F1000 Abstract

64. Zhao YY, Liu Y, Stan RV, et al.: Defects in caveolin-1 cause dilated cardiomyopathy and pulmonary hypertension in knockout mice. Proc Natl Acad Sci U S A. 2002; 99(17): 11375–80. PubMed Abstract | Publisher Full Text | Free Full Text

65. Vogel P, Read R, Hansen G, et al.: Pathology of congenital generalized lipodystrophy in Agpat2-/- mice. Vet Pathol. 2011; 48(3): 642–54. PubMed Abstract | Publisher Full Text | Free Full Text

66. Cauito KM, Lizama CO, Tapia PJ, et al.: Agrp2at is essential for postnatal development and maintenance of white and brown adipose tissue. Mol Metab. 2016; 5(7): 491–505. PubMed Abstract | Publisher Full Text | Free Full Text

67. Fernández-Gaillea M, Tapia P, Cauito K, et al.: Agrp2at deficiency impairs adipogenic differentiation in primary cultured preadipocytes in a non-autophagy or apoptosis dependent mechanism. Biochimie Biomol Res Commun. 2010; 467(1): 39–45. PubMed Abstract | Publisher Full Text

68. Bruder-Nascimento T, Faulkner JL, Haigh S, et al.: Leptin restores endothelial function via endothelial PPPARγ-Nox1 mediated mechanisms in a mouse model of congenital generalized lipodystrophy. Hypertension. In press.

69. Nguyen G, Muller DN.: The biology of the (pre)receptor. J Am Soc Nephrol. 2010; 21(1): 18–23. PubMed Abstract | Publisher Full Text | Free Full Text

70. Takemori K, Gao YJ, Ding L, et al.: Elevated blood pressure in transgenic lipoprotein mice and altered vascular function. Hypertension. 2007; 49(2): 365–72. PubMed Abstract | Publisher Full Text | Free Full Text

71. Kim JK, Gavrilova O, Chen Y, et al.: Mechanism of insulin resistance in A-ZIP/F-1 fatless mice. J Biol Chem. 2006; 281(12): 8456–60. PubMed Abstract | Publisher Full Text

72. Pavlides S, Gutierrez-Pajares JL, Darlot C, et al.: Adipose tissue deficiency results in severe hyperlipidemia and atherosclerosis in the low-density lipoprotein receptor knockout mice. Biochim Biophys Acta. 2016; 1861(1): 410–8. PubMed Abstract | Publisher Full Text

73. Murata T, Lin ML, Huang Y, et al.: Reexpression of caveolin-1 in endothelium rescues the vascular, cardiac, and pulmonary defects in global caveolin-1 knockout mice. J Exp Med. 2007; 204(10): 2373–82. PubMed Abstract | Publisher Full Text | Free Full Text

74. Wang M, Gao M, Liao J, et al.: Adipose tissue deficiency results in severe hyperlipidemia and atherosclerosis in the low-density lipoprotein receptor knockout mice. Biochim Biophys Acta. 2016; 1861(1): 410–8. PubMed Abstract | Publisher Full Text

75. Cipriani S, Francisc O, Mancarelli A, et al.: Efficacy of the CCR5 antagonist maraviroc in reducing early, riluzol-induced arethosenosis and advanced plaque progression in mice. Circulation. 2013; 127(21): 2114–24. PubMed Abstract | Publisher Full Text | Free Full Text

76. Jiang B, Khandelwal AR, Rogers LK, et al.: Adipose tissue deficiency results in severe hyperlipidemia and atherosclerosis in the low-density lipoprotein receptor knockout mice. Biochim Biophys Acta. 2016; 1861(1): 410–8. PubMed Abstract | Publisher Full Text

77. Jones KL, Maggs JL, Davenport AP: Chemokine receptor CCR5: From AIDS to atherosclerosis. Br J Pharmacol. 2011; 162(4): 1453–69. PubMed Abstract | Publisher Full Text | Free Full Text

78. Stein JH, Klein MA, Bellehumeur JL, et al.: Use of human immunodeficiency virus-1 protease inhibitors is associated with atherogenic lipoprotein changes and endothelial dysfunction. Circulation. 2001; 104(3): 257–62. PubMed Abstract | Publisher Full Text

79. Tawakol A, Lo J, Zarrin MV, et al.: Increased arterial inflammation relates to high-risk coronary plaque morphology in HIV-infected patients. J Acquir Immune Defic Syndr. 2014; 66(2): 164–71. PubMed Abstract | Publisher Full Text | Free Full Text

80. Lamouwen-Zepter V, Bornstein SR, Kunos J, et al.: Adrenocortical changes and arterial hypertension in lipoprotein A-ZIP/F-1 mice. Mol Cell Endocrinol. 2008; 280(1-2): 39–46. PubMed Abstract | Publisher Full Text | Free Full Text

81. Gatauffe E, Cohn DM, Poglic M, et al.: Losartan prevents the elevation of blood pressure in adipose-PHR deficient female mice while elevated circulating sPRAV activates the renin-angiotensin system. Am J Physiol Heart Circ Physiol. 2019; 316(3): H506–H515. PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

82. Belin de Chantemelle EJ: Sex Differences in Leptin Control of Cardiovascular Function in Health and Metabolic Diseases. Adv Exp Med Biol. 2017; 1043: 87–111. PubMed Abstract | Publisher Full Text
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2. Frederique Yiannikouris
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