Metabolic complications associated with Lipodystrophic obesity and diabetes

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ABSTRACT

Lipoatrophic diabetes and insulin resistance are typical of lipodystrophy disorders. The discovery of polymorphisms in the monogenic form of the gene has provided us with all the knowledge we currently know about obesity and lipodystrophy. Many factors lead to ailments such as diabetes, cardiovascular problems, hepatic steatosis, and hypertriglyceridemia, including heredity, sedentary lifestyles, and poor diet. The excess fat in the organs makes it difficult for the cells to use glucose, resulting in high blood sugar levels. Lipodystrophies may affect adipokine secretion and/or interaction with stromal cells in adipose tissue. Ultimately, fats get deposited in non-adipose tissue as a result of the inadequacy of subcutaneous adipose tissues to store fat. LPD-induced insulin resistance (adipocytokines) may be caused by an alteration in proteins produced from adipose tissue. Berardinelli-Seip syndrome, also known as lipodystrophy, is characterized by incomplete and unclear adipose tissue at birth or early in life. It can be caused by mutations in any of many genes, including AGPAT2, CAV1, BSCL2, and PTRF. This study examines the relationship between lipodystrophy and both obesity and diabetes. An investigation of thiazolidinedione is currently in progress. The potential treatment for LPD includes insulin-like growth factor-1, leptin, and growth releasing hormone, however, none of these have been approved for treating severe insulin resistance or reducing fat loss caused by LPD.

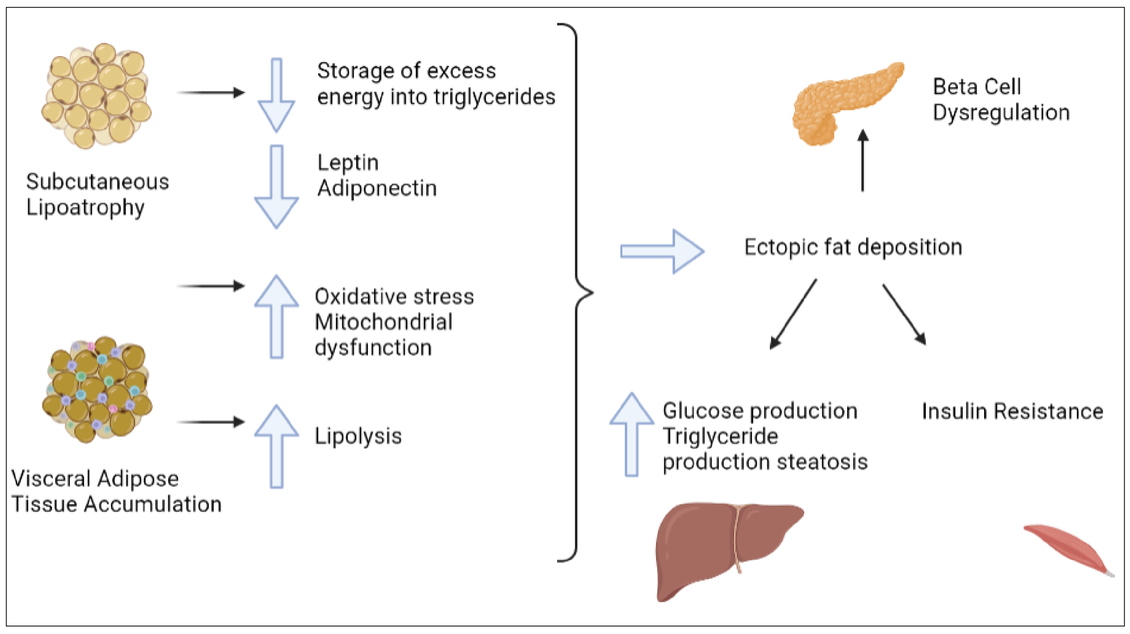
Keywords: lipodystrophy, obesity, diabetes, cell signaling, polymorphism, oxidative stress

INTRODUCTION

Lipodystrophy syndromes are rare diseases characterized by generalized or segmental lack of adipose tissue, and by insulin resistance-related metabolic complications such as diabetes, hypertriglyceridemia, hepatic steatosis, and ovarian hyperandrogenism in women. As well as their different clinical presentations with varying degrees of lipoatrophy, as well as a fat overgrowth in other body areas, lipodystrophies are highly heterogeneous diseases in several other respects. Lipodystrophy syndromes are complex multisystem diseases frequently accompanied by additional clinical signs and complications, including neurologic and cardiovascular involvement. Adipocyte development, differentiation, and/or function are mostly affected by gene pathogenic variants in lipodystrophy syndromes, despite their diversity of clinical forms. Cellular lipotoxicity and metabolic inflexibility strongly impact insulin signaling pathways in lipodystrophy syndromes. By increasing lipid fluxes, hepatic production of triglycerides, glucose, and very low-density lipoproteins is activated, which impairs glucose uptake in the muscles. Physiological consequences of lipodystrophy, such as mitochondrial dysfunction and oxidative stress, also decrease insulin sensitivity.

Adipogenesis, phospholipid biosynthesis, lipid droplet morphology, insulin signaling, caveolins, and lipolysis are all affected by gene mutations causing lipodystrophy. The associated syndrome may be confined to metabolic abnormalities and body fat loss or may result in a spectrum of phenotypes, depending on the particular mutation within the gene.

Figure 1: Metabolic consequences of lipodystrophy



CANDIDATE GENES AND ITS FUNCTIONS

Table 1: Associated genes and its function

Gene Symbol	Gene name	Function
AGPAT2	1-acylglycerol-3-phosphate O-acyltransferase 2	It plays a critical role in the growth and development of adipocytes, which are cells that store fats for energy
CAV1	caveolin 1	This protein appears to have diverse functions in cells and tissues throughout the body.
BSCL2	BSCL2 lipid droplet biogenesis associated, seipin	It is active in cells and tissues throughout the body, particularly in nerve cells that control muscle movement (motor neurons) and in the brain.
PTRF	Polymerase I And Transcript Release Factor	Plays an important role in caveolae formation and organization. Essential for the formation of caveolae in all tissues

CONCLUSION

Lipodystrophy syndromes are rare and heterogeneous diseases. The clinical examination does not systematically examine adipose tissue, and several symptoms are nonspecific, making their diagnosis difficult and potentially delaying. A better understanding of the pathophysiology of these rare diseases may be achieved by using next-generation sequencing technologies with exome or genome analysis. Genetic variants, however, are becoming increasingly difficult to interpret. To explore new pathophysiological determinants of lipodystrophy syndromes and improve patient care, close genetic, clinical, and fundamental research collaborations are essential.

REFERENCES

- Vatier C, Bidault G, Briand N, Guénantin AC, Teyssières L, Lascols O, Capeau J, Vigouroux C. What the genetics of lipodystrophy can teach us about insulin resistance and diabetes. Current Diabetes Reports. 2013 Dec;13(6):757-67.
- Melmed S, Koenig R, Rosen C, Auchus R, Goldfine A. Williams textbook of endocrinology: South Asia edition, 2 vol set-E-book. Elsevier India; 2020 Jun 30.
- Zammouri J, Vatier C, Capel E, Auclair M, Storey-London C, Bismuth E, Mosbah H, Donadille B, Janmaat S, Fève B, Jéru I. Molecular and cellular bases of lipodystrophy syndromes. Frontiers in Endocrinology. 2021;12.

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