Life Without Fat: A Mouse Model of Congenital Generalized Lipodystrophy-related Diabetes

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1 Introduction: Lipodystrophy

- Congenital generalized lipodystrophy (CGL), or Berardinelli-Seip syndrome, is an **autosomal recessive** condition that results from lack of functional adipocytes.
- As a result, **lipids accumulates in ectopic sites**: liver, kidneys, pancreas, skeletal muscles.
- Patients with CGL develop metabolic abnormalities similar to those found in obesity: **Pancreatic beta-cell dysfunction,** hyperinsulinemia & insulin resistance, development of **diabetes mellitus** by the second decade of life, and non-alcoholic fatty liver disease.

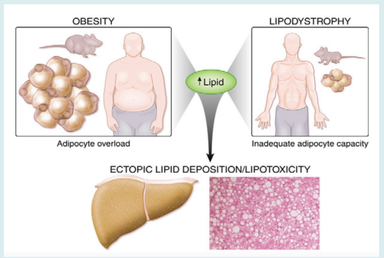
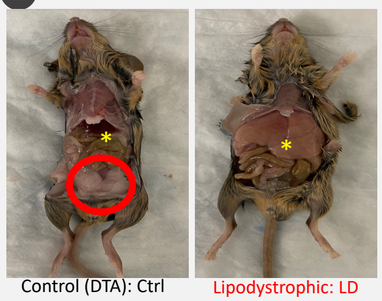


Figure 1. Schematic representing the similarities between obesity and lipodystrophy. Adapted from Savage. *Dis Model Mech* 2009.

2 Generation of LD mice: a good model of CGL



LD mice lacking white and brown fat (**LD**: Lipodystrophy) were generated by breeding DTA mice (**DTA**: Diphtheria Toxin A) with Adiponectin-Cre mice. Upon DTA activation, the diphtheria toxin targeted and eliminated adipocytes.

Figure 2. Comparative images of Ctrl and LD mice on necropsy. LD mice show significant hepatomegaly and fatty liver (starred). Normal white adipose deposits in Ctrl mice (circled) are absent in LD mice.

3 LD mice show increased plasma glucose and plasma insulin

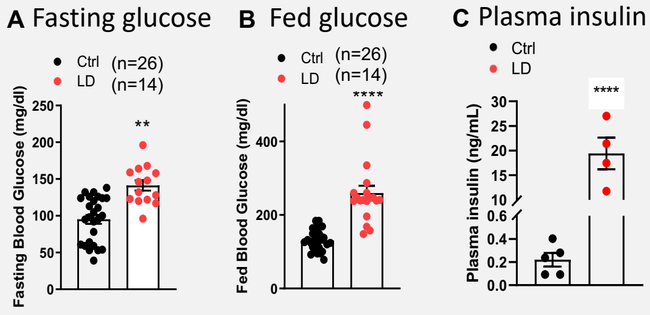


Figure 3. LD mice demonstrated a significant increases in (**A**) fasting (1.82-fold) and (**B**) fed (2.01-fold) blood glucose compared to Ctrl littermate mice. (**C**) ELISA insulin assays showed that LD mice paradoxically had significantly higher plasma insulin concentration than Ctrl mice, explained by the severe insulin resistance of LD mice.

4 LD mice show impaired glucose tolerance and increased insulin secretion

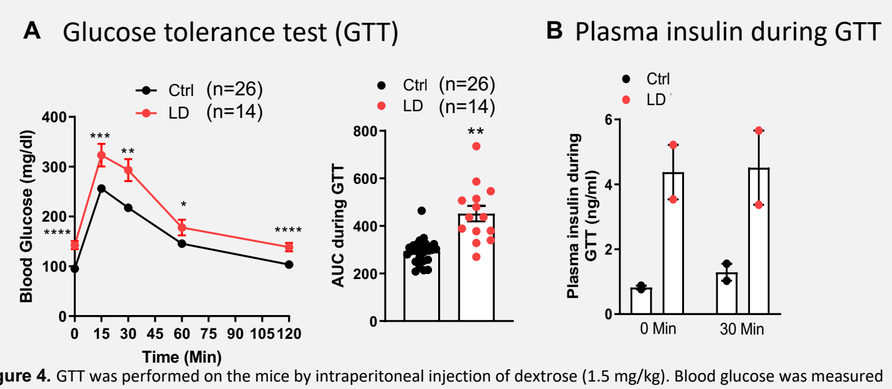


Figure 4. GTT was performed on the mice by intraperitoneal injection of dextrose (1.5 mg/kg). Blood glucose was measured at 0, 15, 30, 60, and 120-minute marks. (**A**) LD mice show impaired glucose tolerance, quantified by the area under the curve (AUC) of the GTT line (middle graph). The larger the area, the more glucose intolerance; LD mice have larger areas. (**B**) Plasma insulin was measured with ELISA on blood collected at time 0, before glucose challenge, and 30 mins into GTT. At 30 minutes, the insulin concentration was higher in both control and LD groups.

5 LD mice are severely insulin resistant

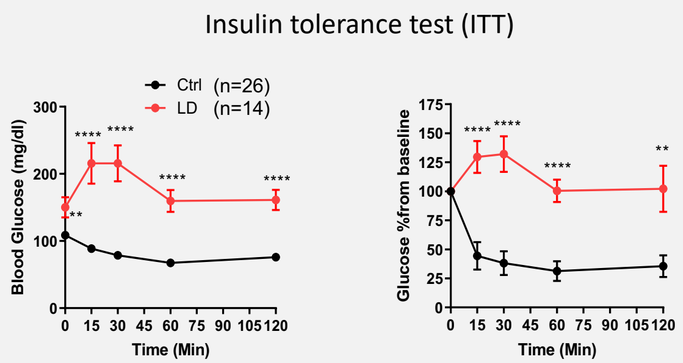


Figure 5. ITT was performed on the mice by intraperitoneal injection of Lantus insulin (0.5U/kg). Blood glucose was measured at 0, 15, 30, 60, and 120-minute marks. The Ctrl mice showed a normal response: blood glucose lowering after insulin administration. LD mice were severely insulin resistant, and their blood sugar even spiked after insulin injection.

6 LD mice have bigger pancreatic islets compared to littermate Ctrl mice

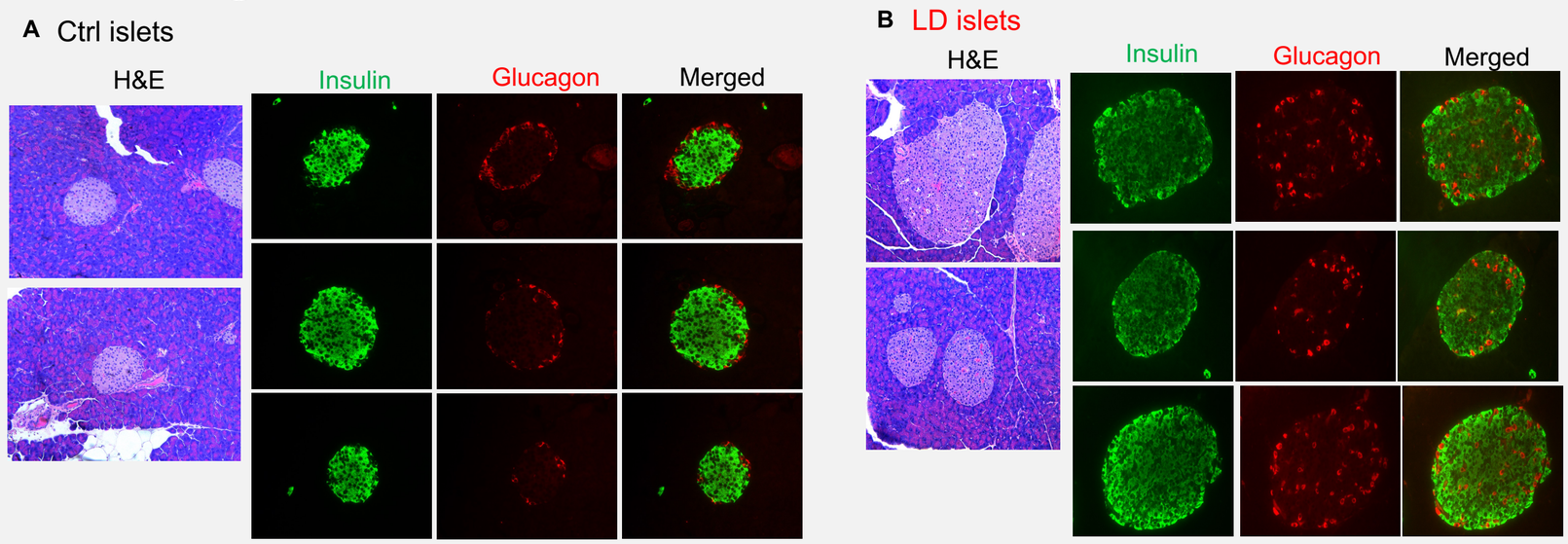


Figure 6. Hematoxylin-Eosin (H&E) and immunofluorescent staining of pancreatic sections demonstrated a marked increase in islet size and higher islet insulin staining in LD mice. In addition, LD islets contained more glucagon-stained alpha cells in the islet core compared to Ctrl.

7 Conclusions and Implications

- In summary, LD mice serve as an excellent model to study lipodystrophy-related diabetes as they demonstrated insulin resistance, glucose intolerance, altered pancreatic islet morphology, hepatomegaly, and ectopic lipid deposits.
- Future studies will aim to gain more insight into the mechanisms underlying temporal progression of diabetes in CGL by determining the contribution of glucose- and lipo-toxicity, changes in genes involved in metabolism, proliferation and islet identity leading to beta-cell exhaustion and failure.
- Of particular interest are the significant liver fat deposits in LD mice– our next projects aim to determine, through qPCR, if liver genes for beta oxidation, lipolysis, and lipogenesis are altered.