

Abstract

Background: In humans, lymphatic dysfunction and obesity appear to have a reciprocal relationship, such that lymphedema can cause adipose deposition, and obesity can impair lymphatic function. Recent studies in mice suggest that obesity induced by a high fat diet impairs lymphatic drainage in the tail and hind limbs. Lymphatics can also become excessively permeable, leaking out lymph in db/db mice, which are obese and diabetic.

Problem: These studies demonstrate lymphatic dysfunction is associated with obesity, however, the pathophysiological mechanisms remain unknown.

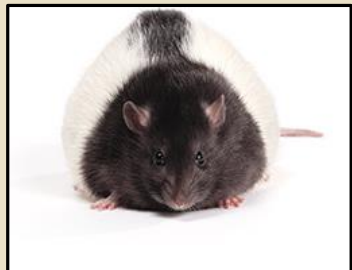
Aim: The goal of this study was to investigate the extent to which obesity gives rise to inflammation and remodeling of the wall of rat mesenteric collecting lymphatic vessels.

Passive wall mechanics: measured using collecting lymphatics isolated and mounted onto resistance-matched glass micropipettes in APSS without Ca^{2+} and luminal pressure stepped from 1-5 cm H_2O .

Crown-like structures (CLSs): Mesenteric arcades with adipose tissue and collecting lymphatics were dissected, fixed in 4% PFA, processed and embedded in paraffin.

Blood-serum and peri-lymphatic adipose tissue (PLAT): were also collected and analyzed for inflammatory biomarkers.

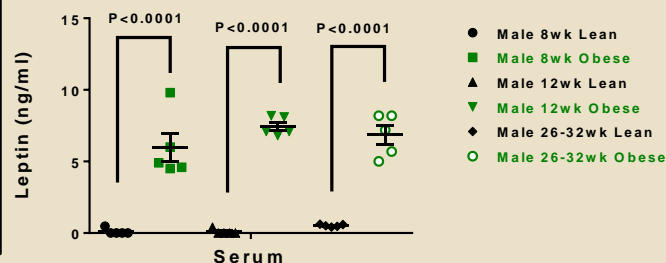
Rat Model of Obesity



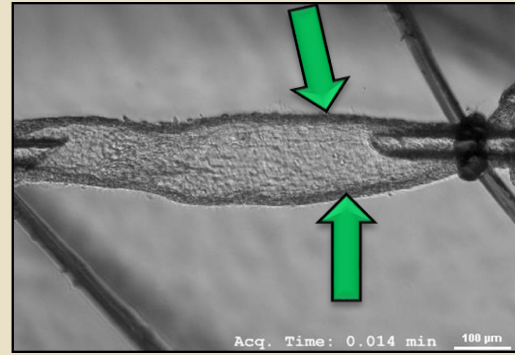
ZUCKER-*Lepr^{fa}*

The obese or fatty condition appeared spontaneously in the 13M strain maintained at the Laboratory of Comparative Pathology of Theodore and Lois Zucker in Stow, MA.

Gene Mutation - Leptin receptor deficiency



Passive Wall Parameters Measured in Mesenteric Collecting Vessels from Male and Female Obese Zucker Rats

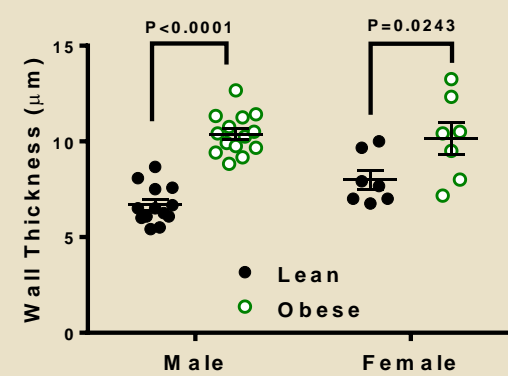


In Ca^{2+} - free APSS
1-5 cm H_2O

Lymphatic wall remodeling involves the reorganization of existing cells and extracellular matrix (ECM) or changes in smooth muscle cell growth and migration. It can be characterized as: **hypertrophic** (increased cross-sectional area), **eutrophic** (no change in cross-sectional area) or **hypotrophic** (reduced cross-sectional area).

Wall Thickness is Increased in Mesenteric Collecting Vessels from Male and Female Obese Zucker Rats

Figure 2. Lymphatic wall thickness in obese and lean Zucker rats. All animals studied to date are included in the means. Data represent Mean \pm SEM.



Mean Elastic Modulus – Measure of the Ability to Recoil in Response to Stretch - Calculated from Stress-Strain Relationships

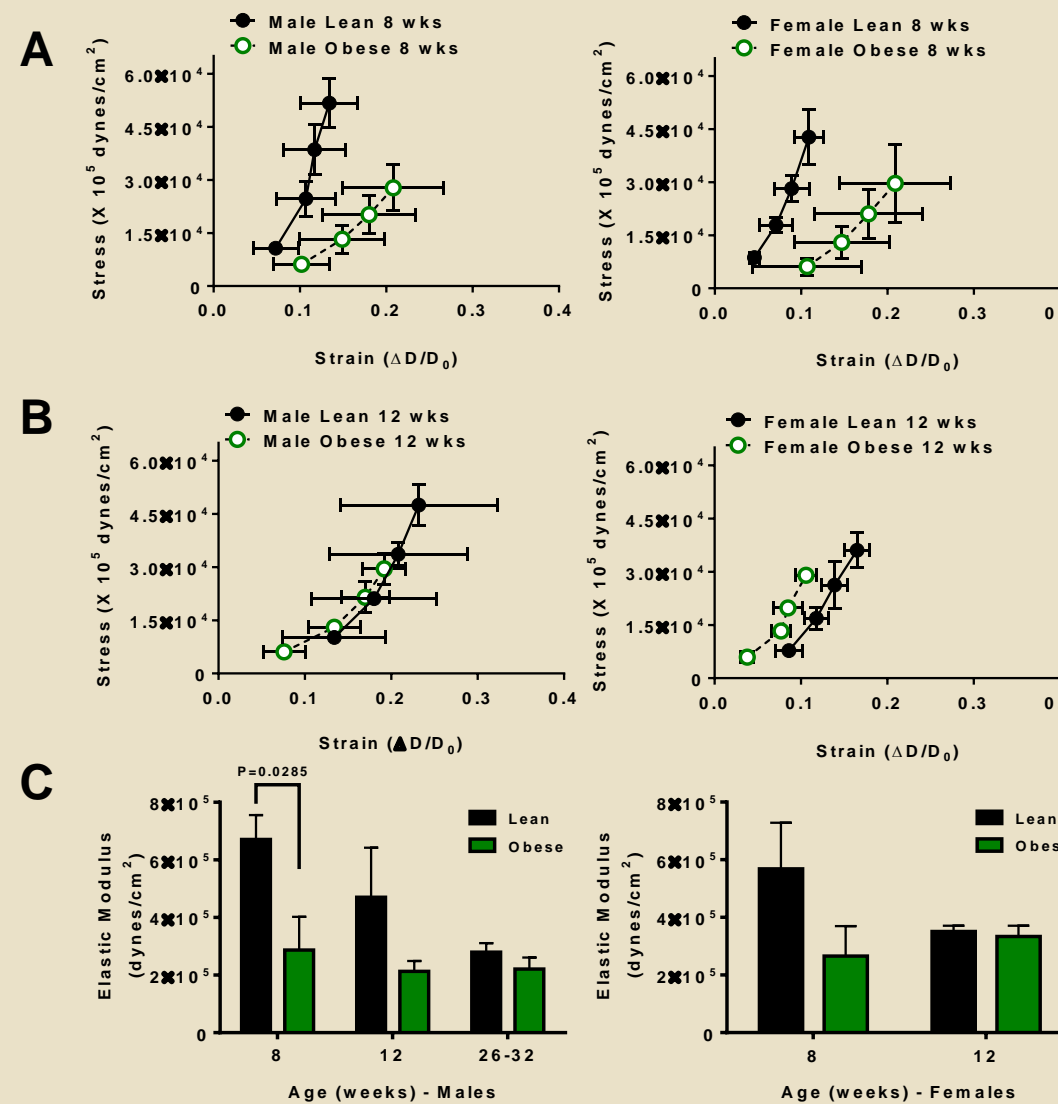


Figure 3. Elastic properties of mesenteric collecting lymphatics in obese and lean rats. (A) Stress-strain relationship for 8-week-old obese and lean male (left panel) and female (right panel) rats. (B) The same comparisons, but with 12-week old rats. (C) Summarized data of elastic modulus calculated from stress-strain relationships of obese and lean rats. The left panel has males that were 8, 12, and 26-32 weeks old (N=5 each group). The right panel has females that were 8 weeks (N=3) and 12 weeks (N=4) old. Data represent Mean \pm SEM.

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Mesenteric Adipose Deposition and Body Weights are Increased in Male and Female Obese Zucker Rats

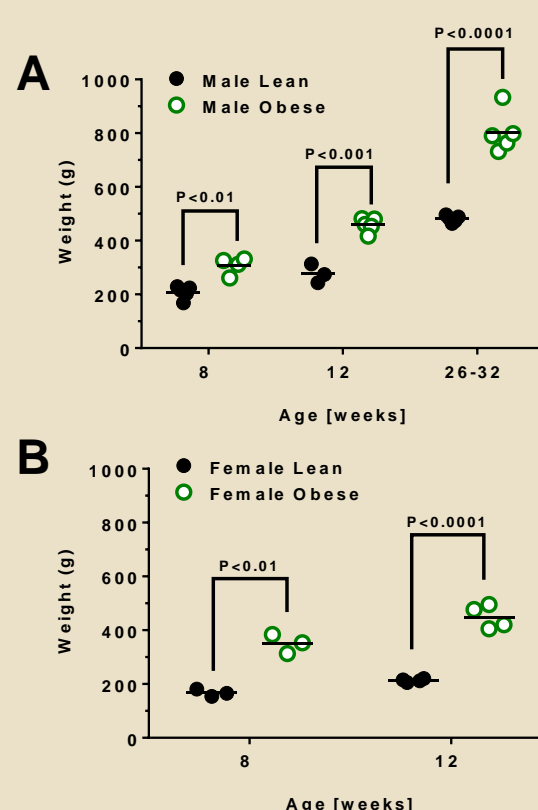
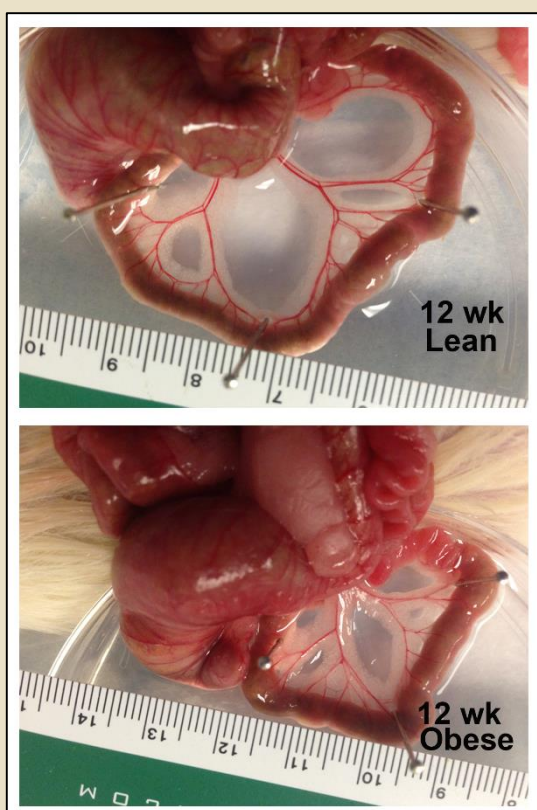


Figure 1. Digital photographs of the terminal ileum from lean and obese male Zucker rats at 12 weeks of age. Panels show increased adipose deposition along the vascular arcades in obese rats. Graphs representing body weights of (A) male and (B) female lean and obese Zucker rats. Data represent Mean; N=3 - 5 rats per group.

Crown-Like Structures in PLAT are Increased in Obese Zucker Rats

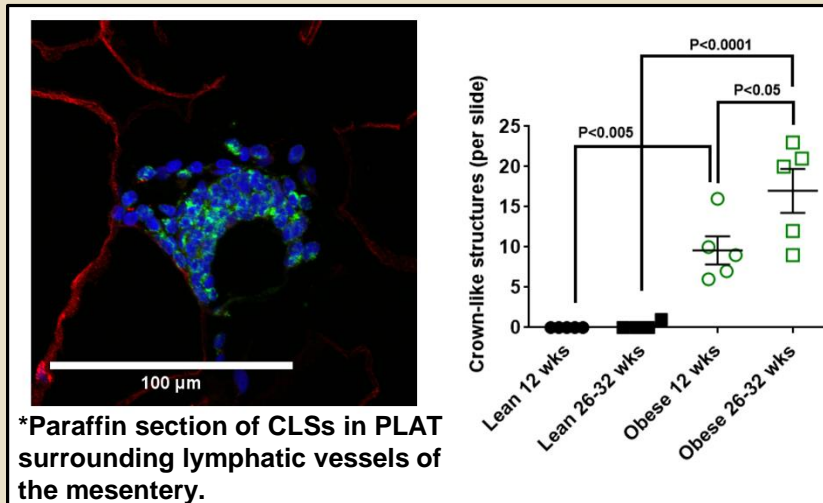


Figure 4. The left panel shows a crown-like structure with macrophages immunolabeled with anti-CD68 and adipocytes immunolabeled with anti-caveolin-1. The right panel shows summarized counts of CLSs in PLAT isolated from lean and obese male Zucker rats aged 12 and 26-32 weeks. Data represent Mean \pm SEM; N=5 rats per group.

Molecular Signals Derived from Adipose and Serum: Contribution to Wall Thickening??

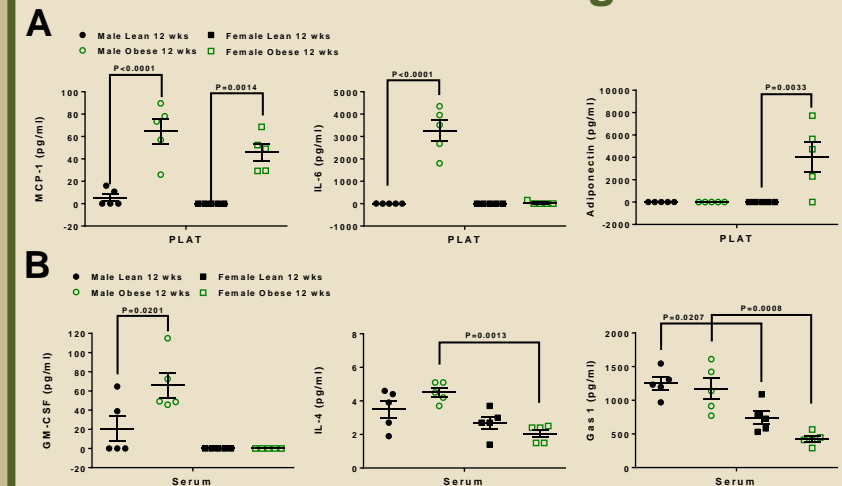


Figure 5. Examples of biomarkers tested for in PLAT (A) and blood-serum (B) isolated from 12 week male and female lean and obese Zucker rats (67 Rat Biomarker Testing Service – RayBiotech). Data represent Mean \pm SEM; N=5 rats per group.

Conclusions

- ❖ Wall thickness is increased in mesenteric collecting lymphatic vessels isolated from obese male and female Zucker rats.
- ❖ The elastic modulus of mesenteric collecting lymphatics normally decreases gradually with age, yet with obesity the loss of elasticity is dramatically accelerated in both male and female Zucker rats.
- ❖ Obesity in the Zucker rat model is associated with both systemic and adipose tissue-associated inflammation. Determining which molecular signals derived from the adipose may be important to understanding the core mechanism(s) of lymphatic wall remodeling observed.