

Sclerostin influences body composition by regulating catabolic and anabolic metabolism in adipocytes

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Introduction

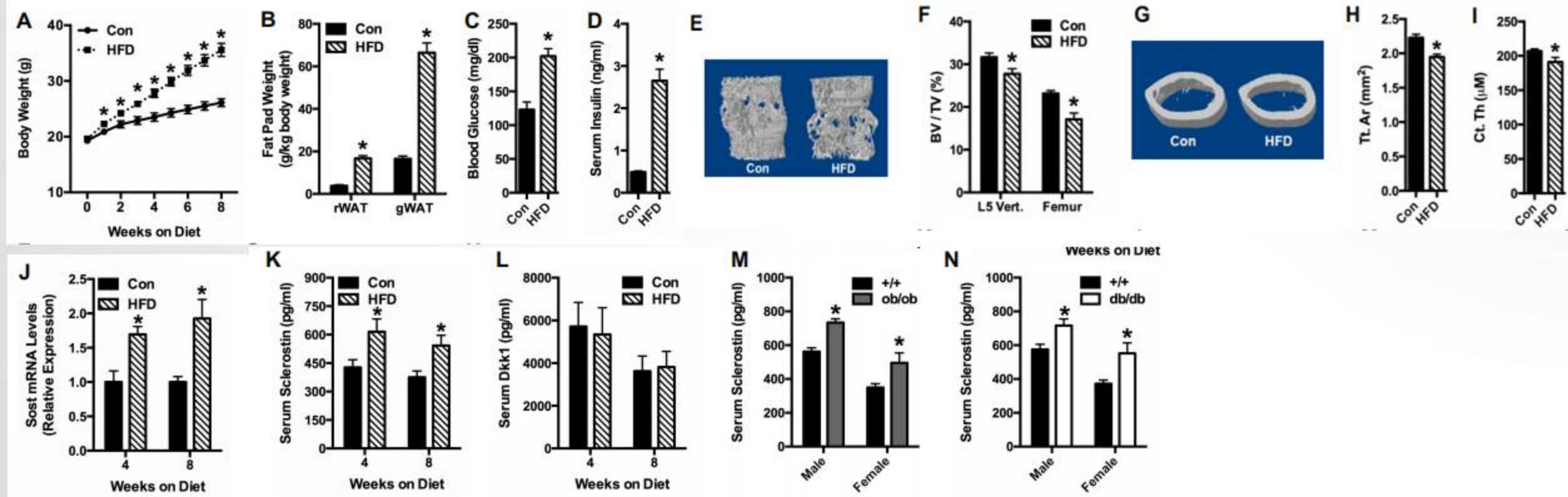
- Skeletal energy requirements are communicated by the secretion of bone-derived hormones that contribute to the coordination of whole-body metabolism.
- Sclerostin, the product of the SOST gene, is a secreted cysteine-knot glycoprotein with homology to the Dan domain family. Produced predominantly by the osteocyte, sclerostin exerts profound control over bone acquisition.
- Sclerostin may influences whole-body metabolism and may do so by influencing Wnt signaling in insulin target tissues.

- The author's results suggest the existence of a bone–adipose interaction wherein sclerostin favors adipogenesis and adipose hypertrophy via the suppression of Wnt signaling and alterations in both catabolic and anabolic metabolism.

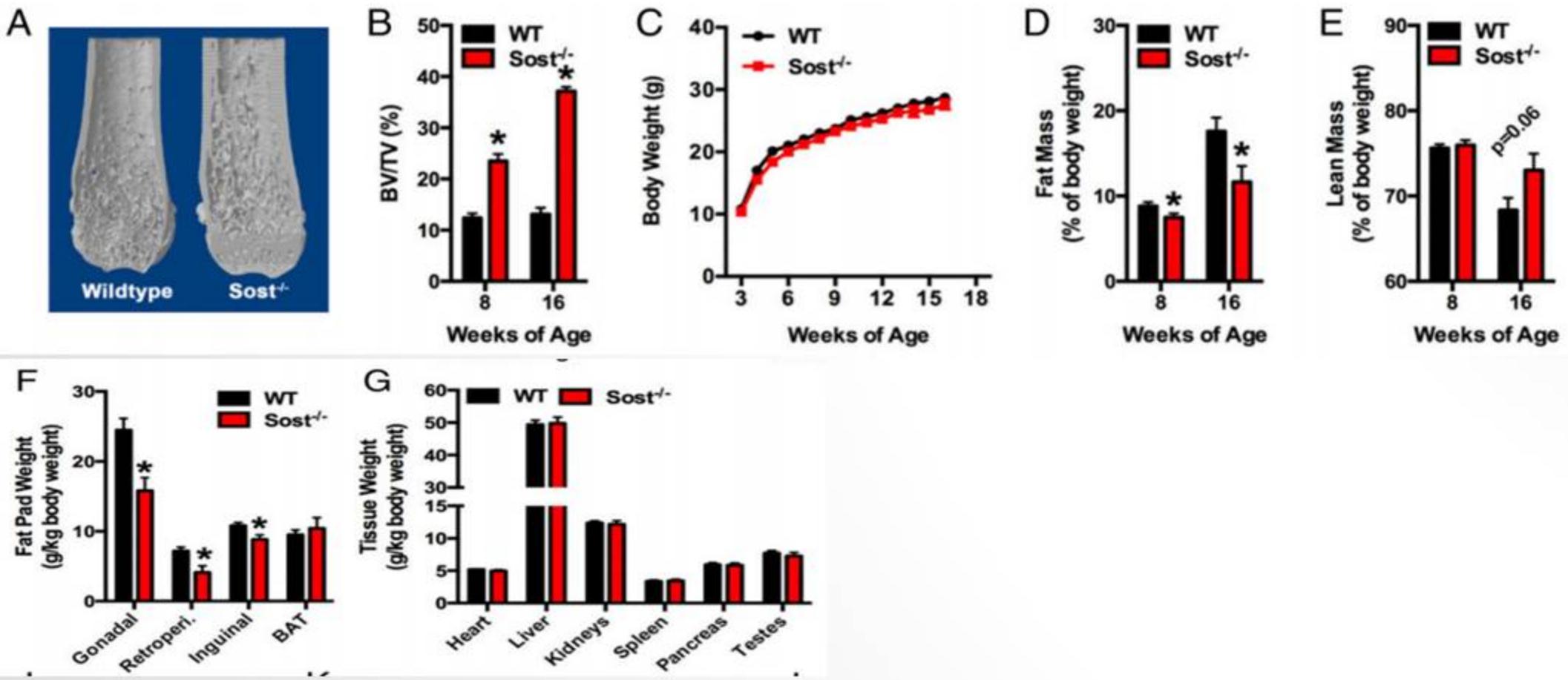
Materials and Methods

- Animals: C57/SOST^{-/-} mice, high-fat diet (HF)/control diet (CON); AAV-Sost and AAV-GFP mice (male C57 mice); ob/ob、db/db mice
- Metabolic phenotyping and bioassays: qNMR (Echo MRI).
- Imaging: mouse femur and L5 vertebra (a desktop micro-tomographic imaging system)
- Cell culture: primary adipocytes (C57BL/6 mice)
- RT-PCR、ELISA、WB

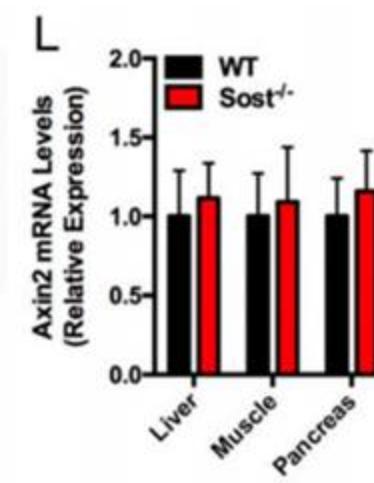
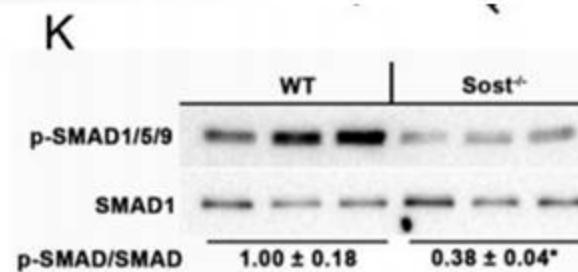
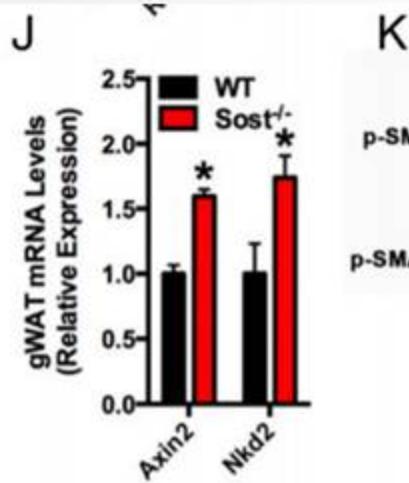
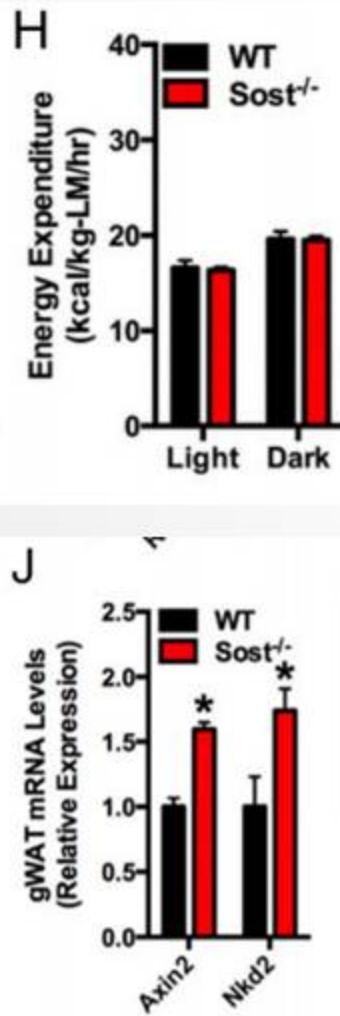
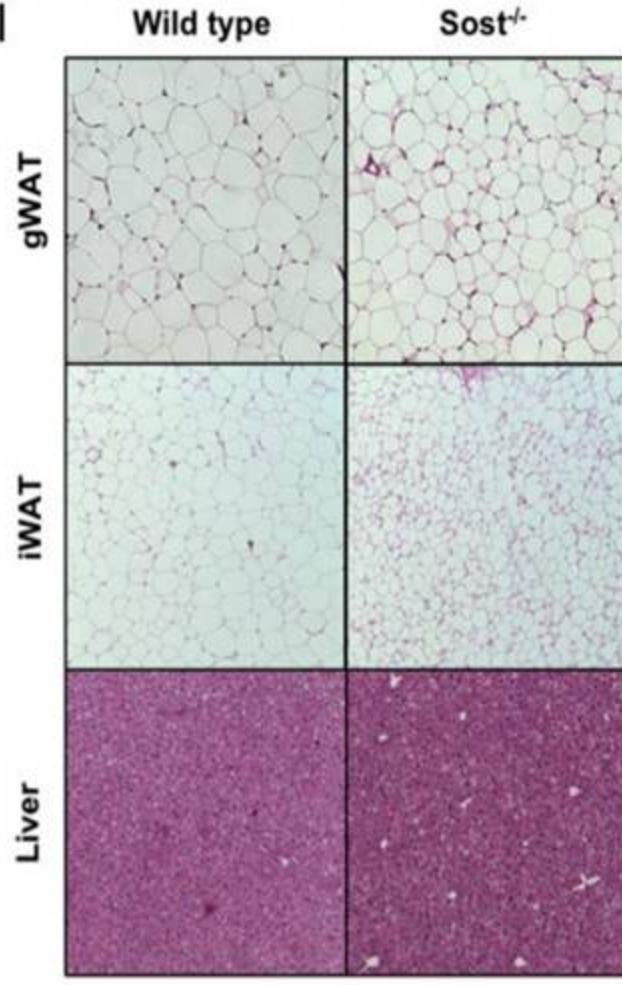
Results



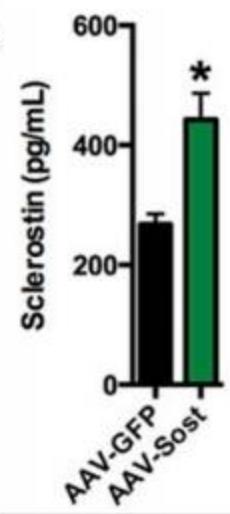
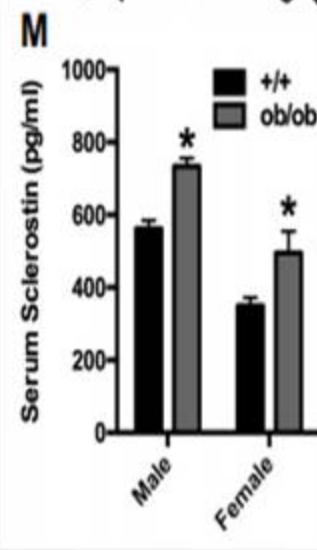
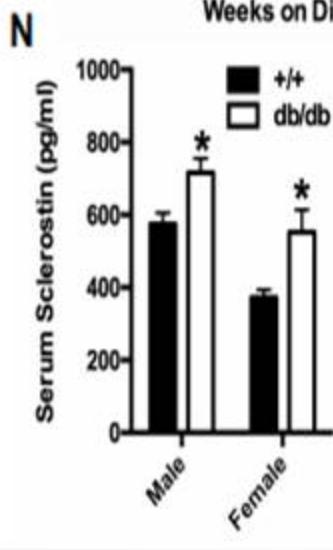
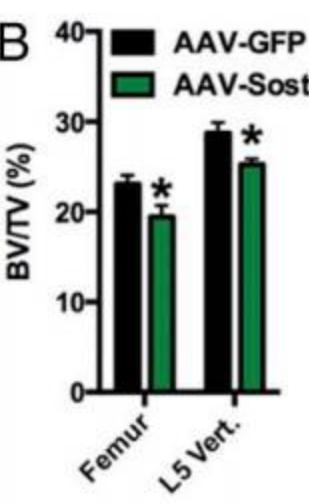
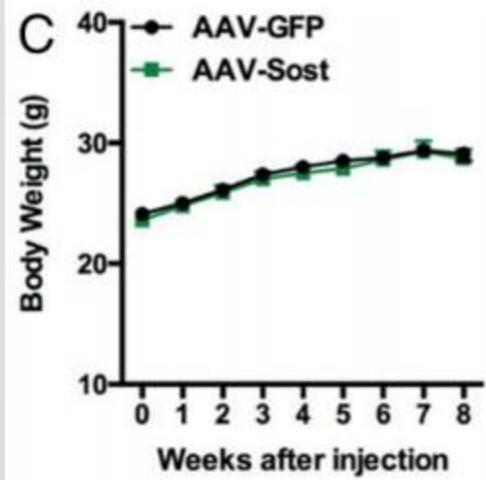
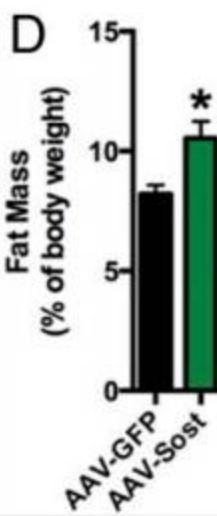
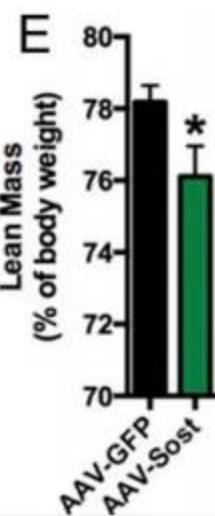
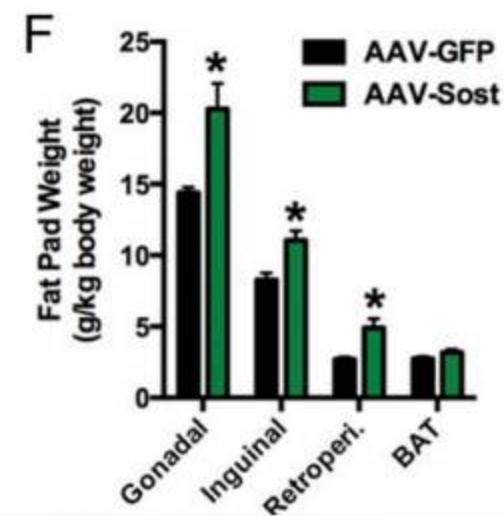
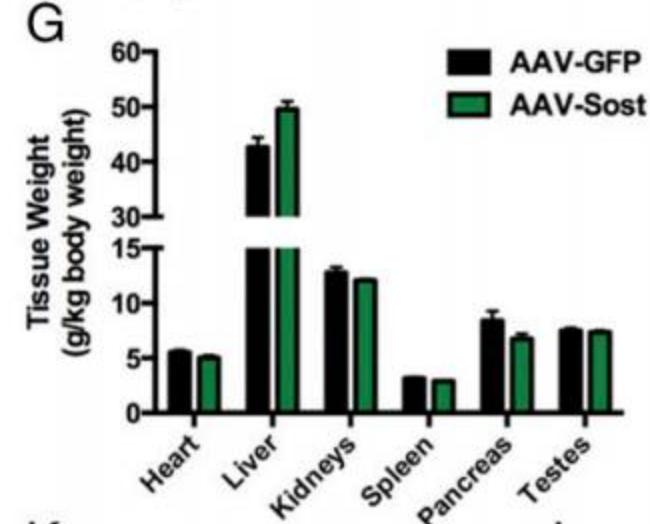
- ▶ High fat diet feeding resulted in an increase in body weight and fat pad mass as well as the development of hyperglycemia, hyperinsulinemia, and osteopenia.
- ▶ These phenotypes were accompanied by significant increases in both Sost mRNA levels in the femur and circulating sclerostin levels.

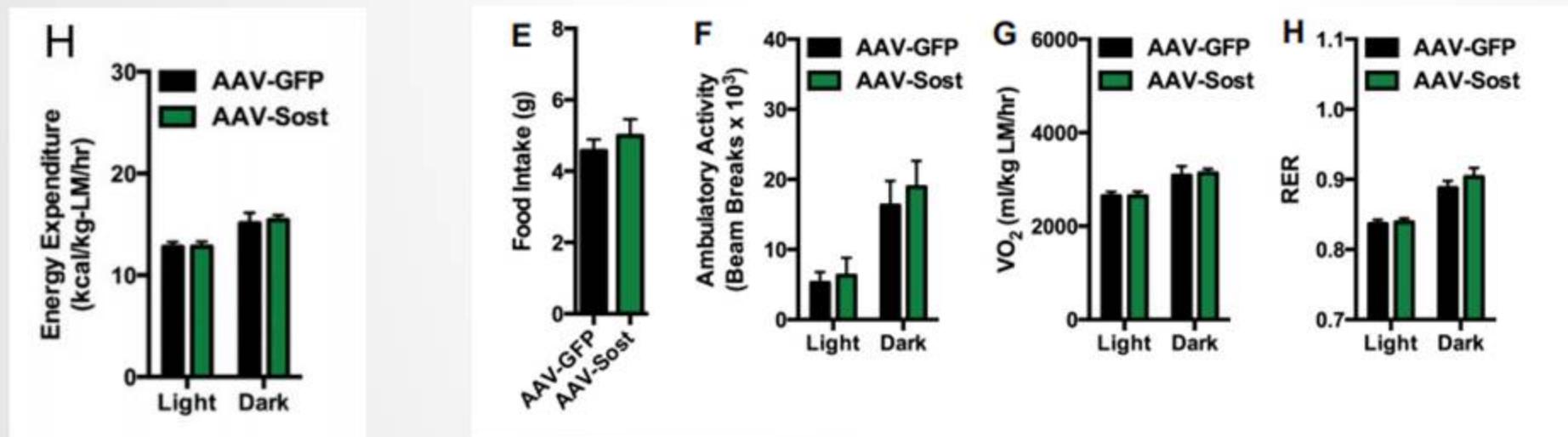


- $Sost^{-/-}$ mice exhibited the expected increases in bone mass and had normal body weight, but qNMR analyses revealed significant reductions in whole-body fat mass and a strong trend toward increased lean body mass fraction in older animals.

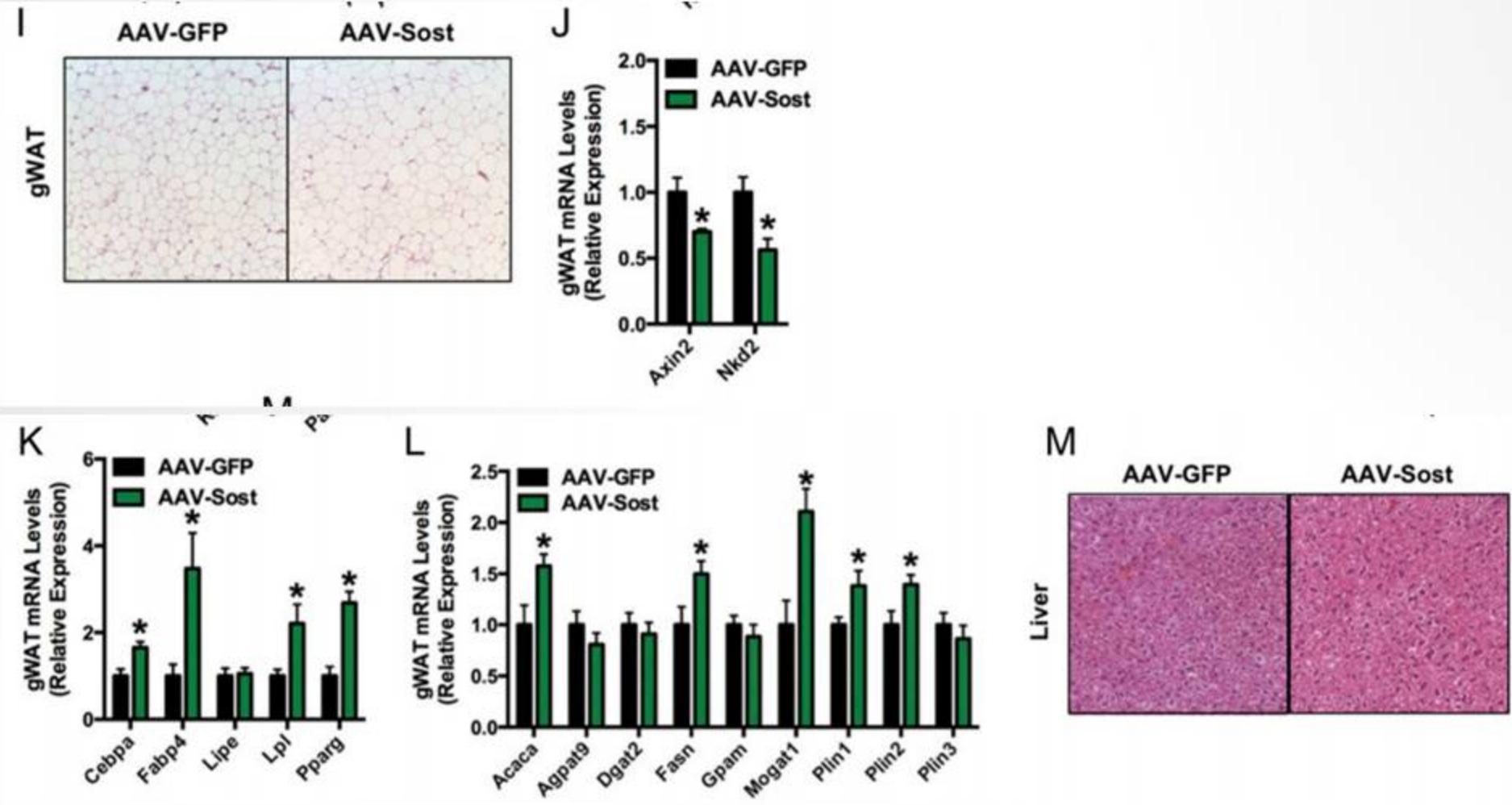


Given the role of sclerostin as a Wnt signaling antagonist and inhibitory effects of Wnt on adipocyte development, we suspected this phenotype might be the result of increased Wnt signaling in white adipose depots.

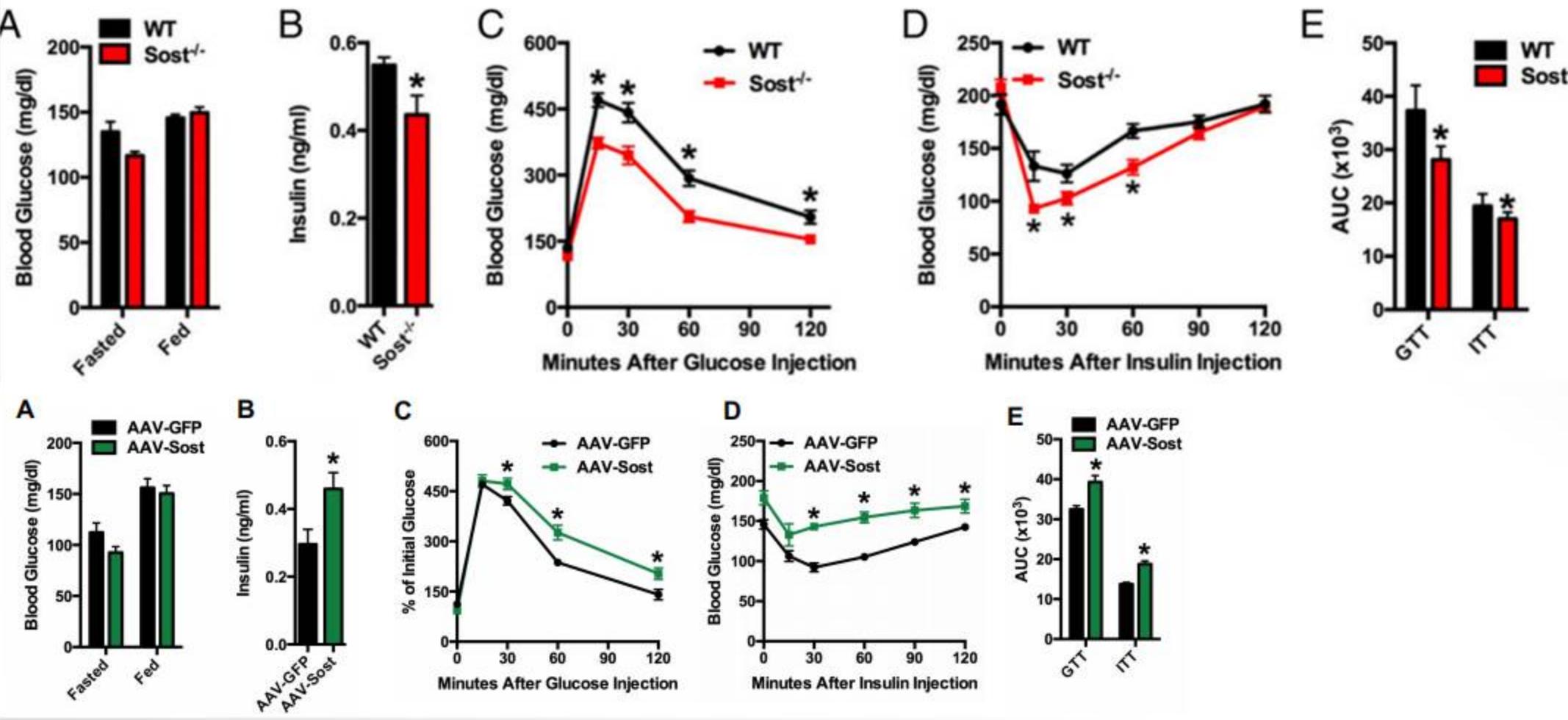
A**M****N****B****C****D****E****F****G**



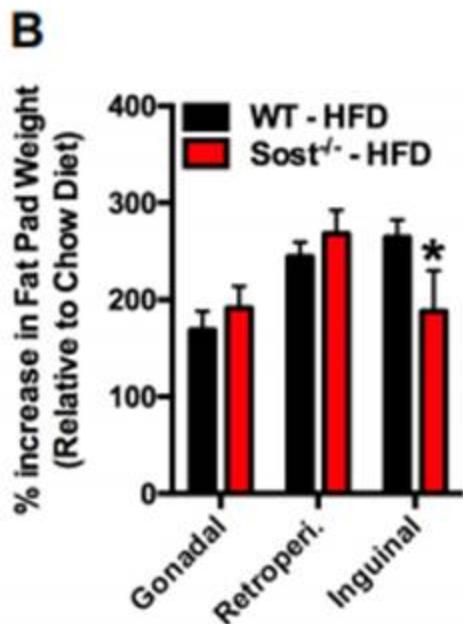
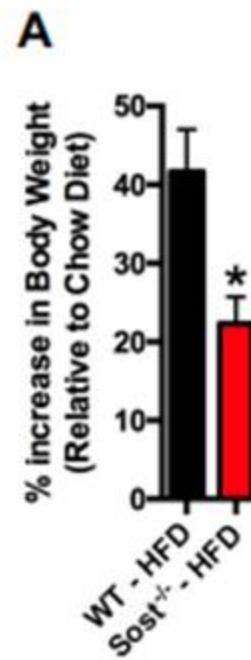
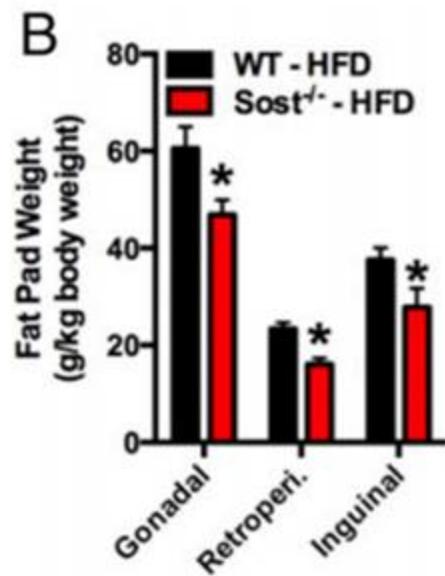
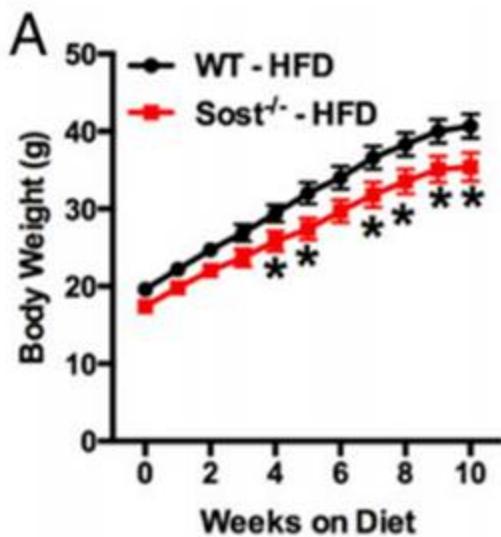
- The overproduction of sclerostin did not influence body weight, but the body composition phenotype of AAV-Sost mice was the opposite of that evident in Sost^{-/-} mice.



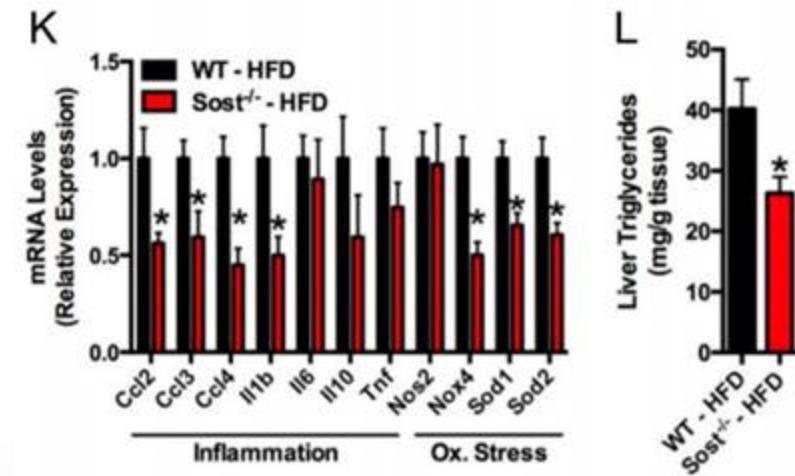
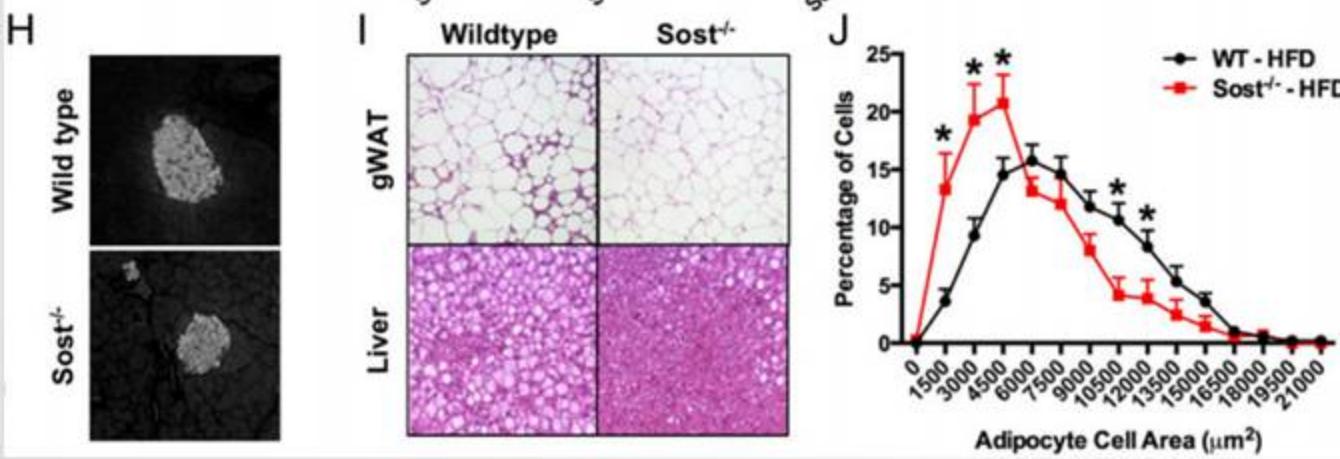
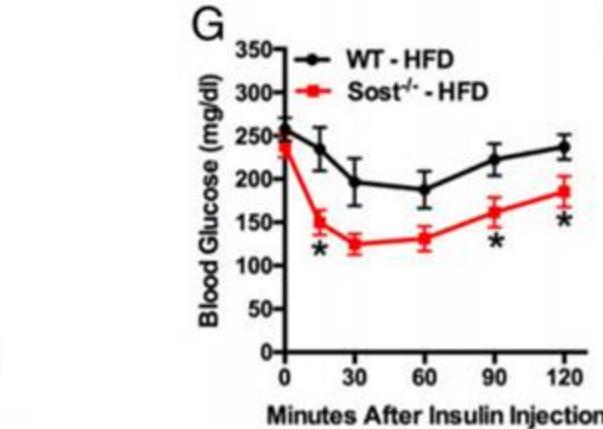
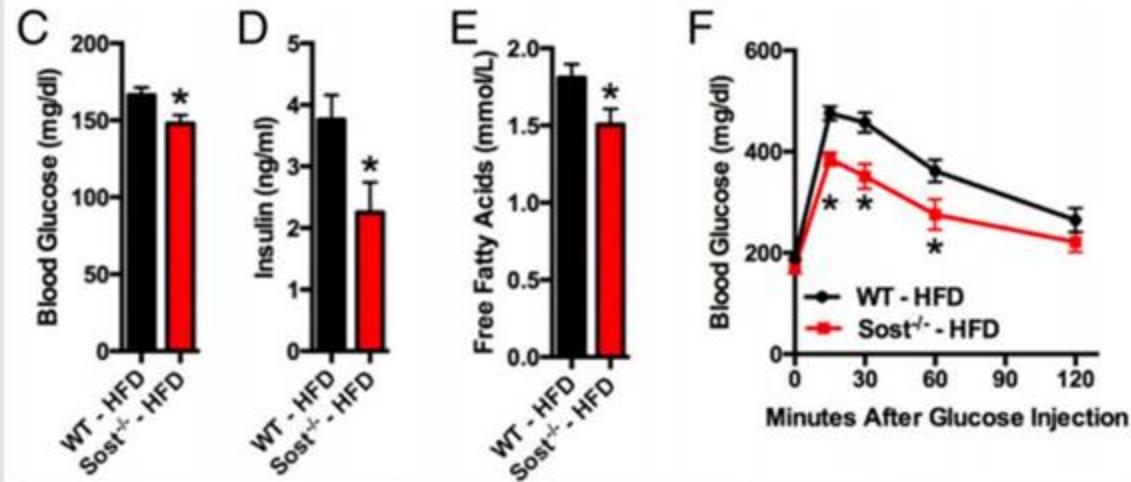
➤ These data imply that sclerostin regulates body composition by facilitating adipocyte differentiation and the synthesis and/or accumulation of triglycerides.



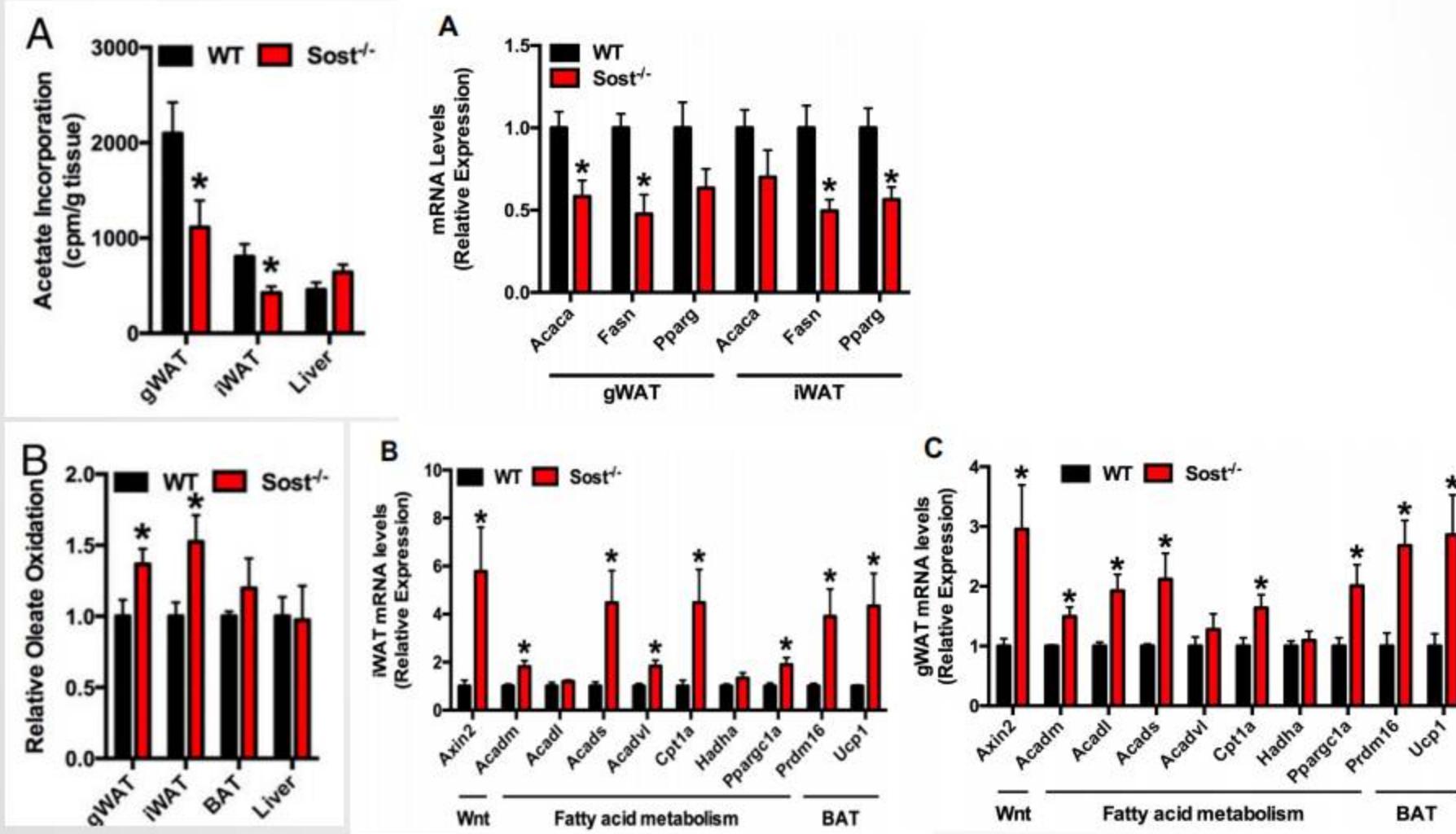
- Sost^{-/-} mice has an increase in insulin sensitivity, by contrast, AAV-Sost mice exhibited deficiencies in parameters of glucose metabolism relative to controls.
- Sclerostin exerts corresponding effects on body composition and lipid and glucose metabolism, presumably by modulating insulin sensitivity in a number of tissues.



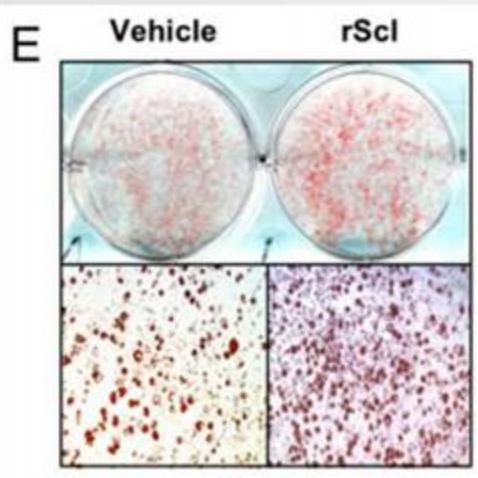
- Sost^{-/-} mice gained significantly less accumulated white adipose tissue weight.



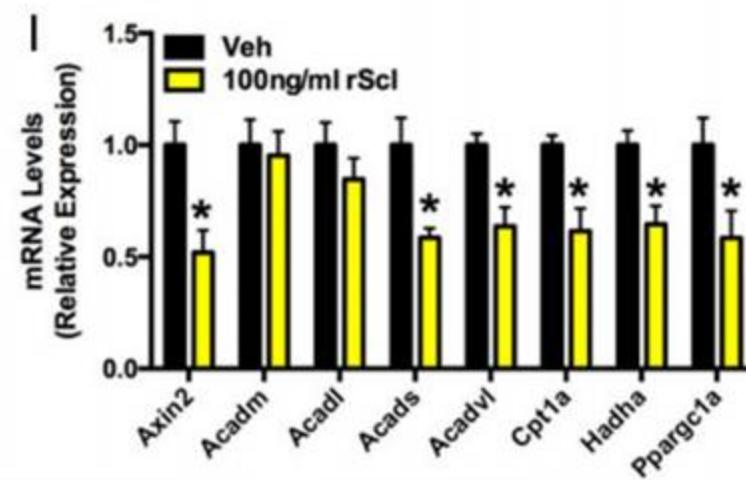
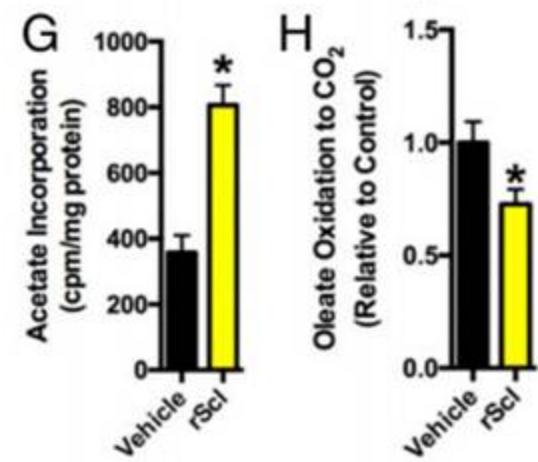
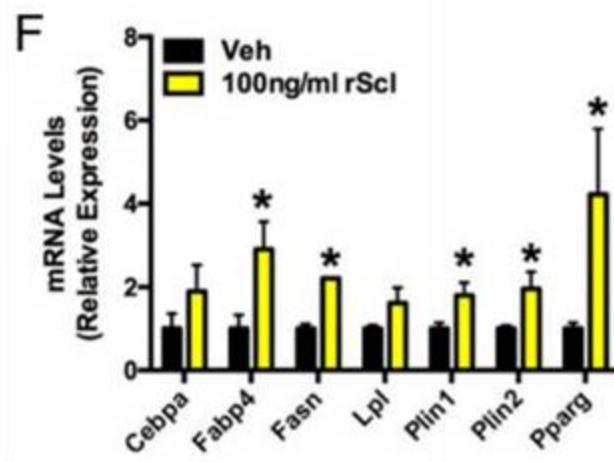
- Sost^{-/-} mice are resistant to the accumulation of body fat and maintain improvements in glucose and lipid metabolism. Moreover, sclerostin deficiency appears to limit inflammation in both the liver and white adipose tissue.

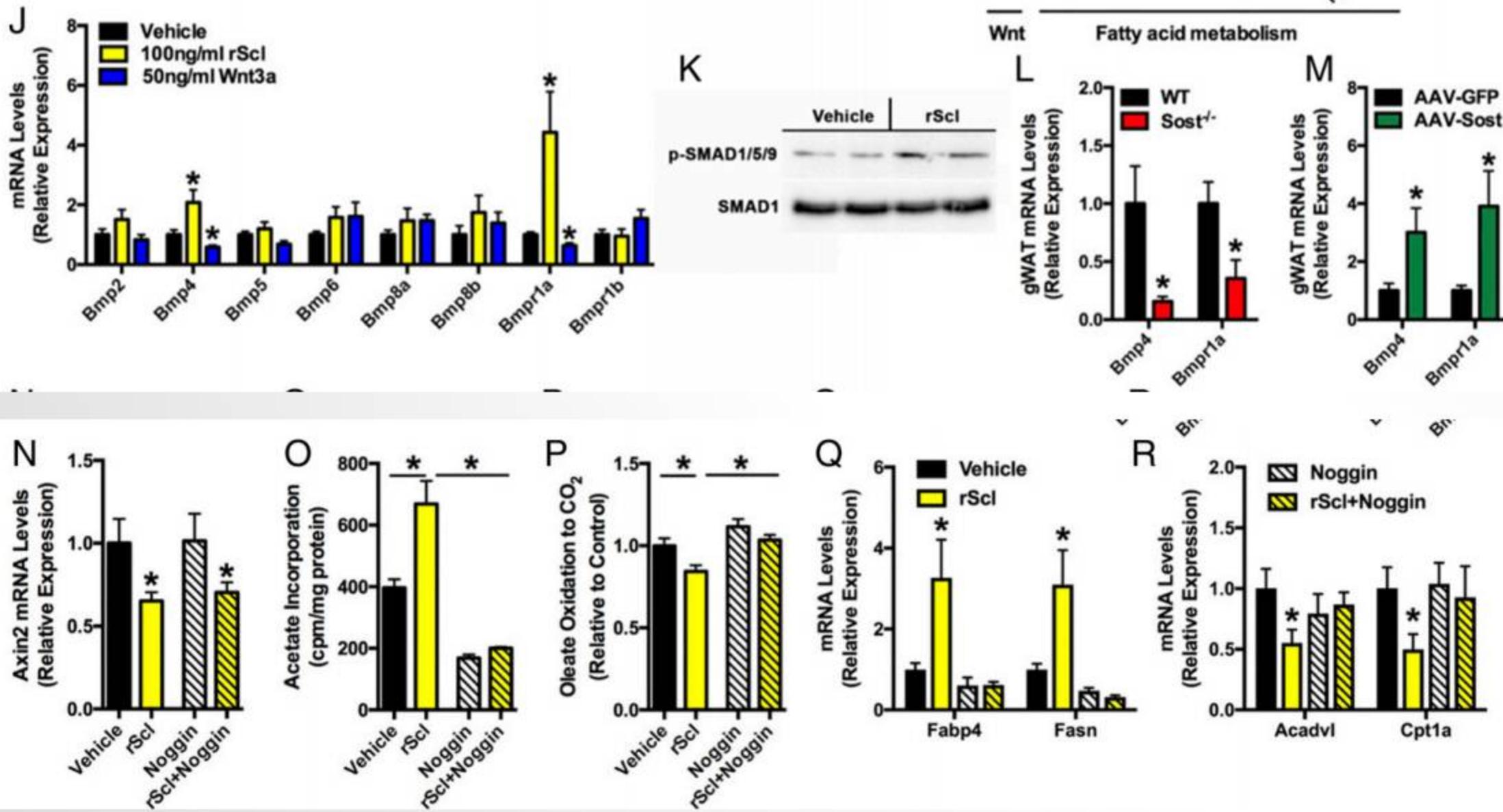


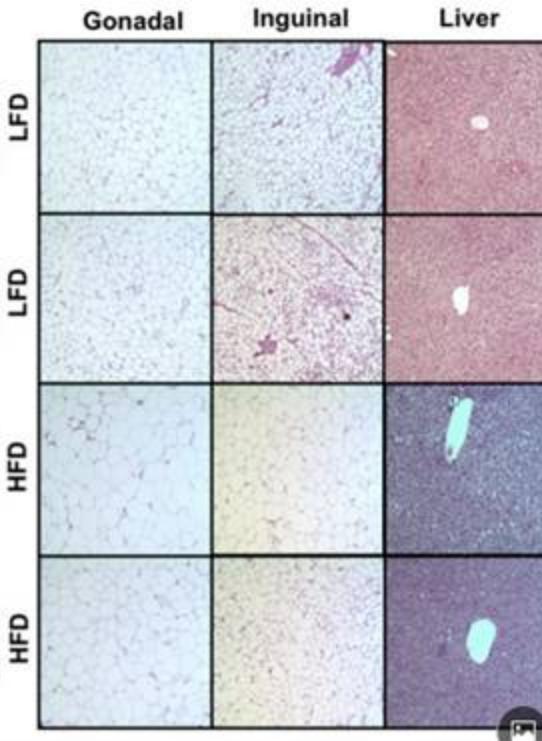
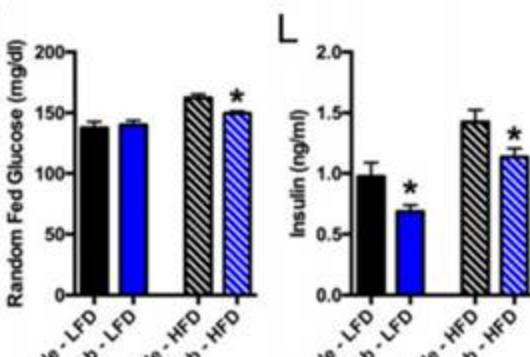
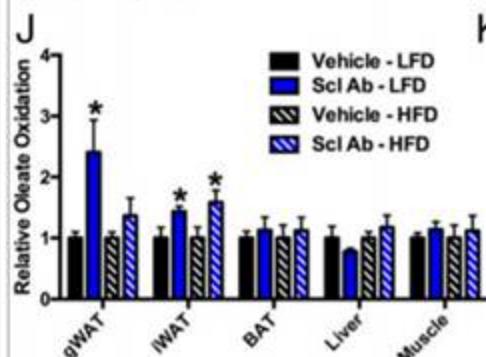
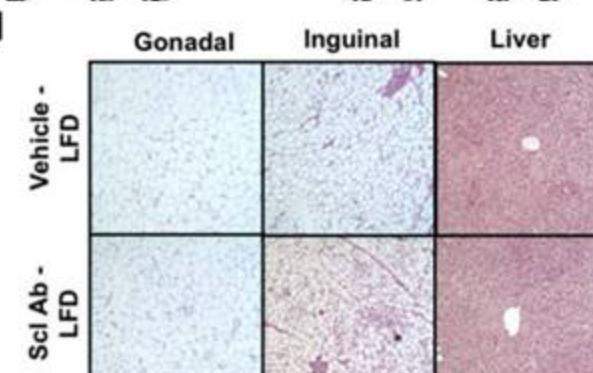
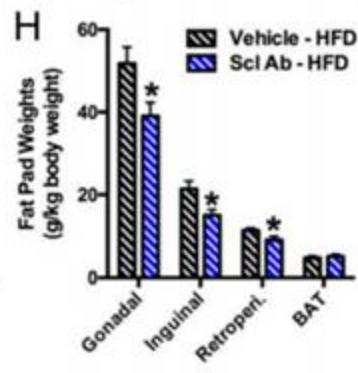
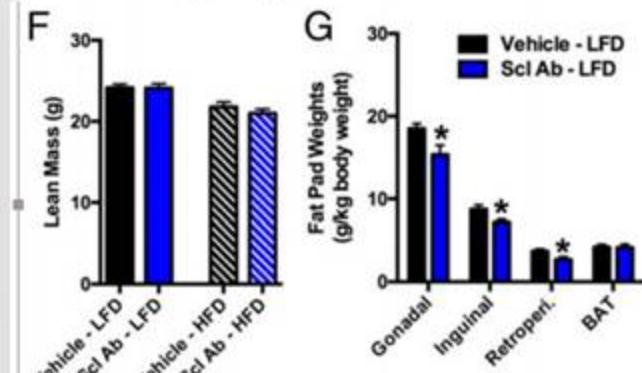
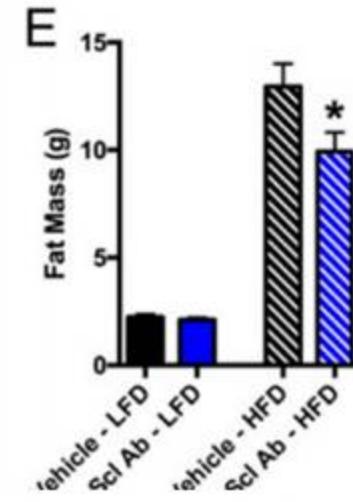
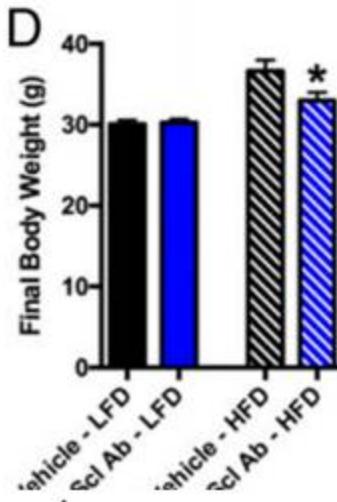
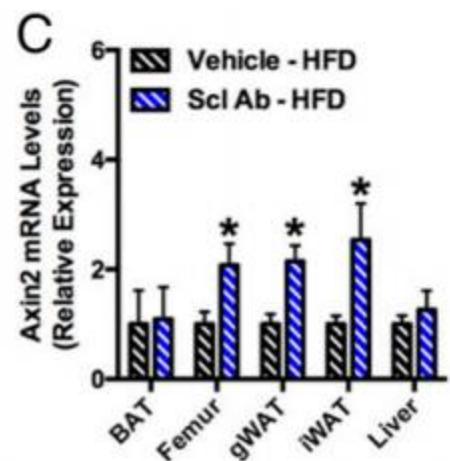
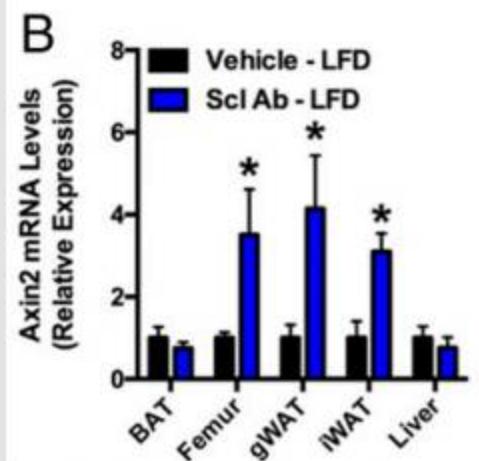
- Compared with controls, fatty acid synthesis, indexed by the incorporation of 3 H-acetate into tissue lipids, was reduced by 53% and 52% in gWAT and iWAT, respectively.



- Recombinant sclerostin treatment also enhanced de novo lipid synthesis and reduced both fatty acid oxidation and the expression of genes associated with fatty acid catabolism.







Discussion

- Due to its dramatic effects on bone acquisition, sclerostin has almost exclusively been viewed as a local inhibitor of skeletal Wnt/β-catenin signaling.
- In this study, the author uncovered a previously unexplored endocrine function for sclerostin, and they attribute these changes in metabolism to alterations in the metabolic function of white adipocytes.
- Mechanistically, the data suggest that sclerostin exerts its effects on adipocyte metabolism by indirectly regulating Bmp signaling.

Thank you

