IMPAIRED ADIPOSE TISSUE INFLAMMATION RESULTS IN INCREASED BONE MASS

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Background

Bone and fat are linked in many ways. For example, adipocytes are found in the bone marrow and expansion of bone marrow adipose tissue is often associated with low bone mass, possibly because adipocytes and osteoblasts competitively differentiate from the same stem cell. Impaired adipose tissue inflammation results in low adipogenesis and metabolic disturbances, which suggests that inflammation within adipose tissue is essential for healthy adipose tissue expansion. If adipose tissue inflammation affects bone mass is however unknown.

Aim: The aim of this study was to test the hypothesis that impaired adipose tissue inflammation, causing low adipogenesis, results in high osteogenesis and bone mass by using RID transgenic (tg) mice.

Conclusion: Mice with impaired adipose tissue inflammation and low adipogenesis had higher bone mass and strength than wildtypes. However, the effect was delayed in females. The osteogenesis remains to be investigated.

Results

Figure 1. Total and lumbar BMD was increased in RID tg mice
Male RID tg mice had higher total BMD at 4 (+5%), 8 (+5%), and 11 (+4%) weeks of HFD, as well as higher lumbar BMD at 4 (+11%), 8 (+17%), and 11 (+8%) weeks of HFD compared with wildtypes **(A-B)**. For female mice, the bone phenotype was not apparent until 11 weeks of HFD, when female RID tg mice had higher lumbar (+17%), but not total, BMD than wildtypes **(C-D)**.

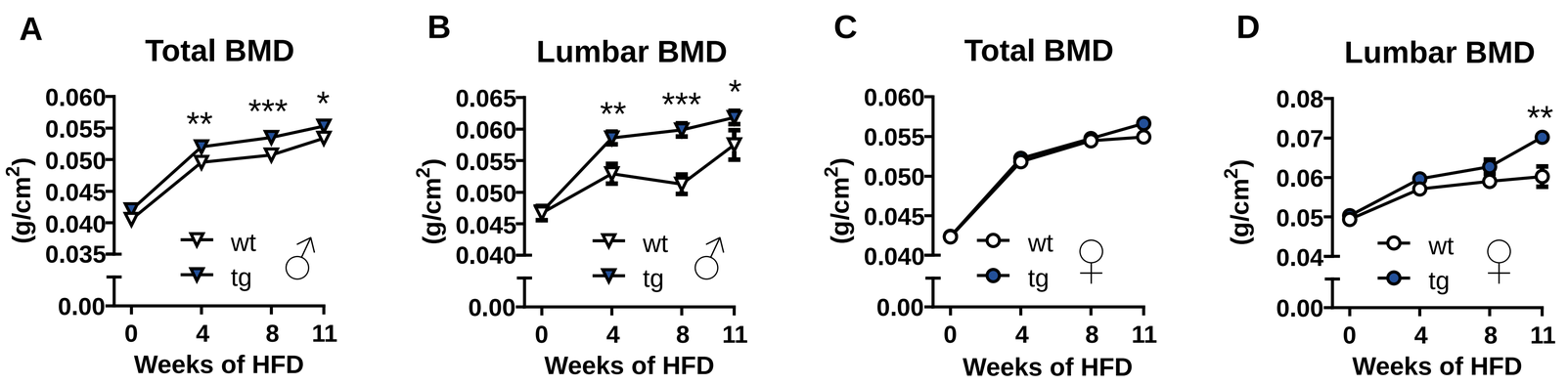


Figure 2. Trabecular and cortical bone mass and bone strength was increased in RID tg mice after 11 weeks of HFD
Male RID tg mice had higher femoral trabecular BMD (+9%), cortical content (+10%), and cortical thickness (+6%) than wildtypes **(A-C)**. Female RID tg mice had higher femoral trabecular BMD (+11%), cortical content (+8%), and cortical thickness (+7%) than wildtypes **(A-C)**. Bone strength measurements of humeri indicated that male and female RID tg mice had higher bone strength (+44% and+47% respectively) than wildtypes **(D)**.

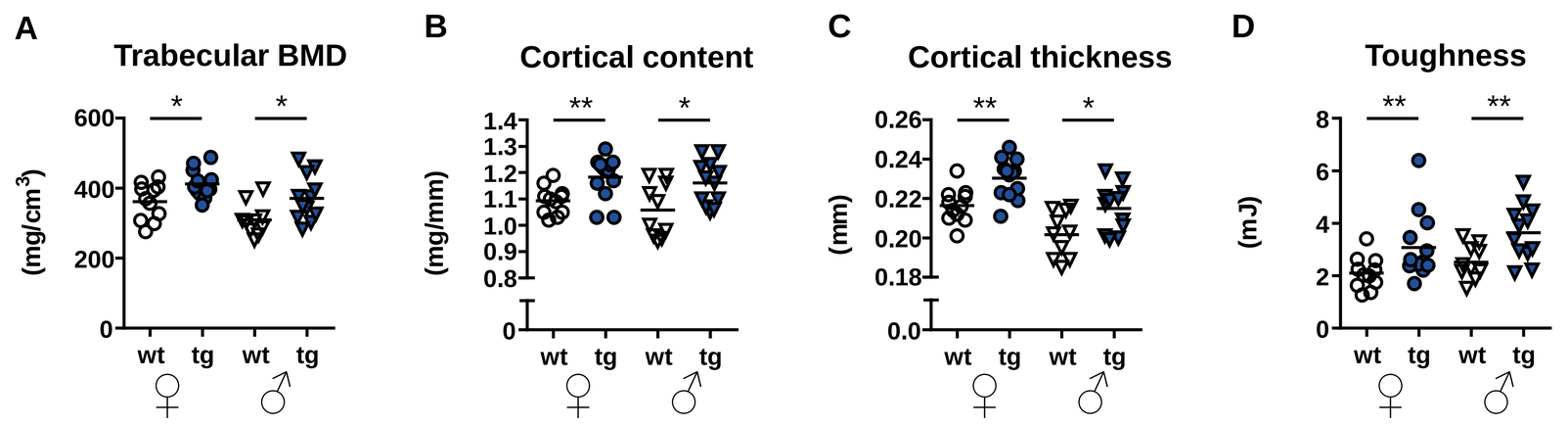
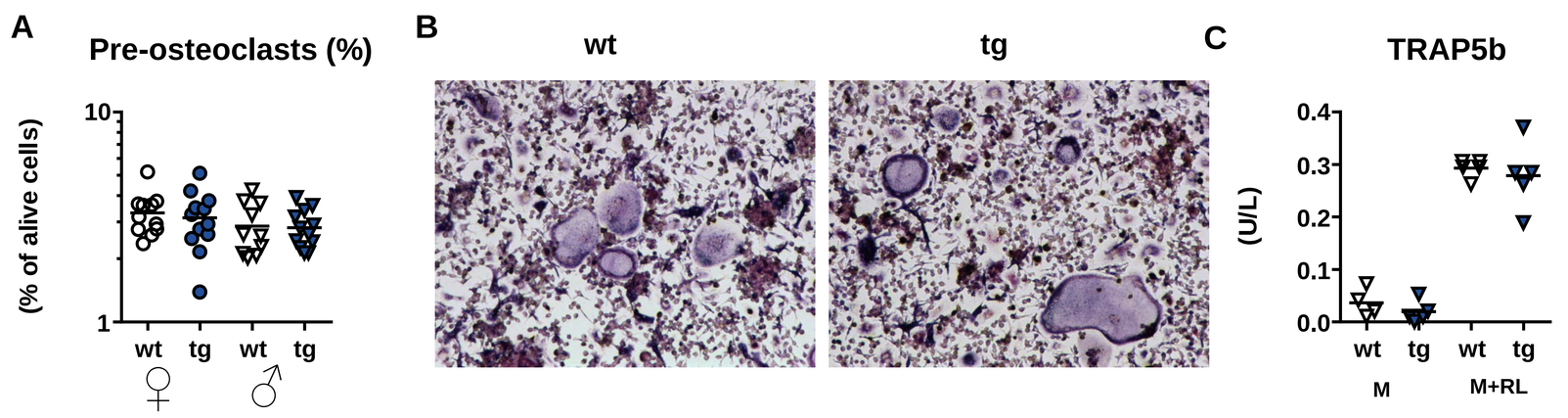


Figure 3. Pre-osteoclasts frequencies *in vivo* and osteoclast differentiation *ex vivo* do not differ
Frequencies of bone marrow pre-osteoclasts ($CD11b^+F4/80^+Gr\text{-}1^-MCSF\text{-}R^+$ cells) did not differ between groups, as measured by flow cytometry **(A)**. Osteoclast differentiation was unaffected *ex vivo*, as judged by the number of TRAP stained multinucleated cells at day 4 **(B)** and the similar levels of TRAP5b in the culture media from bone marrow macrophages cultured in M-CSF (M) or M-CSF and RANKL (M+RL) **(C)** from chow fed wildtypes and RID tg mice.



Methods

RID tg mice overexpress an adenoviral protein complex, RID, that suppress inflammatory signalling in adipocytes and they have impaired adipose tissue inflammation with low adipogenesis (Wernstedt Asterholm *et al.* Cell Metab 20, 1-16, 2014). RID tg and wildtypes were fed high fat diet (D12492, Research Diets) to induce the need for adipose tissue expansion. See timeline for further information.