Sclerostin Deficient Mice Display Sarcopenia But Also Resistance To Bone Loss During Hind Limb Suspension.

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Introduction: While the absence of mechanical load results in skeletal muscle and bone loss, little is known regarding the interaction of bone and muscle during the absence of mechanical load. To address this gap in knowledge we examined changes in bone and muscle in mice deficient in Sost, the gene that encodes sclerostin. Previous studies have shown Sost knockout (KO) mice were resistant to unloading induced bone loss by hind limb suspension (HLS) (1) as were mice given sclerostin antibody (2). To explore possible interactions between muscle and bone during unloading, we examined the hypothesis that both bone and muscle from Sost KO mice are resistant to HLS induced atrophy.

Methods: Mice (4m male C57Bl/6J) globally deficient in Sost (Sost KO), and wild type (WT) controls were exposed to HLS or maintained in control cages for 2 weeks (4 groups, n=7-9/group). Mice were subjected to baseline and endpoint µCT scans. Total body weight and quadriceps weight were recorded and percent muscle and fat quantified by 1H-NMR. Protein synthesis was determined using the [3H]-L-phenylalanine flooding dose technique.

Results: At baseline, Sost KO mice displayed significantly greater trabecular and cortical bone volume relative to WT. Decreases in several bone parameters following 2 weeks of unloading were significantly attenuated in Sost KO (Fig.1). Sost KO displayed reduced loss of trabecular BV/TV (-2% vs. -39%, p<0.05), cortical BV/TV (-0.5% vs. -10%, p<0.05) trabecular thickness (+5% vs. -28%, p<0.05), and trabecular number (+8% vs. -13%, p<0.05). Trabecular connectivity density was also significantly altered in unloaded Sost KO mice versus WT (+27% vs. -17%, p<0.05).

All mice were of similar weight at the start of study; however, Sost KO displayed significantly more adipose tissue and less lean tissue than WT mice (Fig. 2). HLS resulted in a further gain of fat and loss of muscle in Sost KO, and also resulted in decreased quadriceps weight in WT (Fig. 3). Quadriceps weight was decreased in Sost KO controls relative to WT controls but did not decrease further after HLS. Phosphorylation of S6K1, a downstream substrate of mTOR which is a central regulator of protein synthesis, was significantly reduced in both WT and Sost KO HLS compared to controls (Fig. 3). Muscle protein synthesis in WT HLS mice was significantly decreased relative to WT controls. Sost KO control mice showed significantly less protein synthesis when compared to WT controls; Sost KO HLS mice did not show a decrease in protein synthesis (Fig. 3).

Discussion: These are the first studies to examine skeletal muscle in Sost KO mice exposed to unloading induced bone loss. While Sost KO gained bone and were resistant to unloading, they displayed dramatic sarcopenia and increased adiposity relative to WT controls. Furthermore, decreased protein synthesis was a consequence of Sost deficiency alone. Previous studies did not observe sarcopenia in mice given anti-sclerostin antibody for three weeks nor were these mice resistant to HLS-induced muscle loss (2).
**Significance:** Our results suggest that long-term sclerostin deficiency, while having positive effects on bone, may have deleterious effects on muscle. If confirmed, these findings should be considered when developing therapeutic protocols using sclerostin antibody.

![Graph](image)

*Figure 1. Percent change from baseline for trabecular and cortical BV/TV (letter changes indicate significant difference).*
Figure 2. Baseline body composition measurements for wild-type and Sost KO mice (letter changes indicate significant difference).
Figure 3. Phosphorylation of S6K1, an mTOR effector and regulator of total protein synthesis in the quadriiceps (left), and total protein synthesis in quadriiceps (right) (letter changes indicate significant difference).