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Traumatic Brain Injury Leads To Deteriorated Bone Structure Through Increased Adrenergic Signaling

Trauma / Varia Trauma

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Background
Patients with traumatic brain injury (TBI) have higher mortality rates and suffer from cognitive deficits, physical disabilities and neurodegenerative diseases. Additionally, a broad range of pathophysiological dysregulations leads to increased morbidity. In the recent years, there has been growing evidence that the bone metabolism is strongly affected by TBI, leading to reduced bone density and biomechanical inferiority. In previous studies, we were able to reproduce this phenomenon in a murine model. However, the underlying mechanism remained unknown.

Objectives
Our objective was to identify the molecular pathways leading to impaired bone quality following TBI.

Study Design & Methods
18 female 12-week-old C57Bl/6J mice received a traumatic brain injury (controlled cortical impact injury model). Gene expression analysis in the femur and adipose tissue was performed at 3, 7 and 14 days after trauma. To investigate the impact of the adrenergic signaling, 20 mice of the same age were treated with 5mg/kg/d norepinephrine or sodium chloride as control through a subcutaneously implanted pump and bone structure of the femur and humerus was analyzed 21 days later using micro-CT. Biomechanical stability of the femur was examined 21 days after intervention in a torsional test.

Results
In line with the reduced mechanical stability of the femur of TBI-treated mice, we observed a downregulation of osteoblast-specific genes like *Alpl, Col1a1* and *Osteocalcin* in the bone three days following TBI, pointing towards an inhibition of bone metabolism that normalized within 14 days. Serum measurements and increased expression of target genes in adipose tissue revealed an increased adrenergic signaling in TBI-treated mice, representing a central pathway of brain-bone crosstalk. Therefore, we suggested norepinephrine to transmit this inhibitory effect on the bone metabolism. Consistently, the healthy mice that were treated with norepinephrine showed an impaired quality and biomechanical stability

of the bone.

Conclusions

We characterized the negative effect of TBI on the intact bone on gene expression level in our murine model and proved that increased adrenergic signaling, as present following TBI, impairs bone structure and stability. These results underline, that traumatic injuries, which are associated with increased sympathetic tone and therefore increased adrenergic signaling, strongly impair the bone quality of the patients, leading to osteoporosis. Bone health evaluation should be an important part of the follow-up care for these patients.