



## PEER-REVIEW REPORT

**Name of journal:** *World Journal of Orthopedics*

**Manuscript NO:** 90067

**Title:** Exercise promotes osteogenic differentiation by activating the long non-coding RNA H19/microRNA-149 axis

**Provenance and peer review:** Unsolicited Manuscript; Externally peer reviewed

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**Reviewer's code:** 03372482

**Position:** Editorial Board

**Academic degree:** MD, PhD

**Professional title:** Academic Research, Professor

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**Reviewer chosen by:** Lin Zhang

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Scientific quality	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input checked="" type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Novelty of this manuscript	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Good <input type="checkbox"/> Grade C: Fair <input type="checkbox"/> Grade D: No novelty
Creativity or innovation of this manuscript	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Good <input type="checkbox"/> Grade C: Fair <input type="checkbox"/> Grade D: No creativity or innovation



<b>Scientific significance of the conclusion in this manuscript</b>	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Good <input type="checkbox"/> Grade C: Fair <input type="checkbox"/> Grade D: No scientific significance
<b>Language quality</b>	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
<b>Conclusion</b>	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input checked="" type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
<b>Re-review</b>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<b>Peer-reviewer statements</b>	Peer-Review: <input type="checkbox"/> Anonymous <input checked="" type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

#### SPECIFIC COMMENTS TO AUTHORS

**BACKGROUND** Regular physical activity during childhood and adolescence is beneficial to bone development, as evidenced by the ability to increase bone density and peak bone mass by promoting bone formation. **AIM** This study was designed to investigate the effects of exercise on bone formation in growing mice and to investigate the underlying mechanisms. **METHODS** 20 growing mice were randomly divided into two groups: Con group (control group, n=10) and Ex group (treadmill exercise group, n=10). Mice in the Ex group were forced to undergo treadmill exercise for 8 weeks. HE staining, immunohistochemistry, and micro-CT scanning were used to assess the bone formation-related indexes of mouse femur. Subsequently, BMSCs from Con and Ex group mice were extracted to explore the potential mechanism of lncRNA H19-mediated exercise to promote osteogenic differentiation of BMSCs. Bioinformatics analysis was used to find potential miRNAs targets of lncRNA H19. RT-qPCR, Western Blot and cell transfection were used to confirm potential miRNA target genes of lncRNA H19 and the role of lncRNA H19 in promoting osteogenic differentiation. In addition, the expression of autophagy-associated protein markers such as Beclin1, P62, and LC3B was assayed

using immunofluorescence and Western Blot techniques to explore the potential link between exercise-promoted osteogenesis and autophagy. **RESULTS** Compared with the Con group, the femoral growth plate of mice in the Ex group was significantly thickened, and the expression of the osteogenic differentiation marker BMP2 was also significantly increased, suggesting active osteogenesis. The micro-CT results showed that 8w moderate-intensity treadmill exercise significantly increased bone mineral density (BMD), bone volume fraction (BV/TV), and the number of trabeculae (Tb.N), and decreased trabecular segregation (Tb.Sp) in the femur of mice. Inhibition of lncRNA H19 significantly upregulated the expression of miR-149 and suppressed the expression of markers of osteogenic differentiation such as ALP, Runx2 and BMP2. In addition, knockdown of lncRNA H19 significantly downregulated the expression of autophagy markers such as Beclin1 and LC3B, suggesting that autophagy is inhibited when osteogenic differentiation is impaired, which is consistent with the results of autophagy-related protein changes detected in mouse femurs by immunofluorescence.

**CONCLUSION** Appropriate treadmill exercise can effectively stimulate bone formation and promote the increase of bone density and bone volume in growing mice, thus enhancing the peak bone mass of mice. The lncRNA H19/miR-149 axis plays an important regulatory role in the osteogenic differentiation of BMSCs. Exercise may promote bone formation in mice through the lncRNA H19/miR-149 axis, which may be related to the activation of autophagy. In General: it's a good paper and the subject of the manuscript is applicable and useful. Title: the title properly explains the purpose and objective of the article Abstract: The abstract should be one paragraph with 150-250 words. It should emphasize the analytics model used in the study, the data, the results, and the novelty of the proposed approach. You need to expand the acronyms in the abstract upon the first use. Minimize acronyms. Stick to the point and make that point power- fully. Tell the reader what your research is about, what methods you used, and



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