

Universitätsklinikum Carl Gustav Carus

Medizinische Klinik und Poliklinik III

Direktor: Prof. Dr. med. S. R. Bornstein

Bereich Molekulare Knochenbiologie

Leiterin: Prof. Dr. scient. med. M. Rauner



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Universitätsklinikum
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Opponents review on the PhD thesis of Mgr. Benova

Student: Mgr. Andrea BENOVA

Title: Effect of obesity and metabolic complications on molecular characteristics of bone marrow skeletal stem cells in relation to bone and adipose tissue metabolism

The presented dissertation investigates the effect of dietary and pharmacological interventions on obesity-induced bone loss. To date, there are no specific treatment options to improve bone health in obesity or diabetes. As such, this thesis addresses an important research question.

Mgr. Benova shows that treatment of mice on a high-fat diet (HFD) with PUFAs (omega-3 polyunsaturated fatty acids) improved their bone health and reduced bone marrow adiposity. Further, improved bone health was also observed after treatment with a novel thiazolidinedione analogue (MSDC-0602K). The latter in particular improved cellular respiration and differentiation of osteogenic cells by stimulating glutamine metabolism, providing new insights into mechanisms of action that might be amenable to therapeutic targeting, either using the described interventions, or potentially new ones.

Overall, Mgr. Benova presents an excellent dissertation. She introduces the topic comprehensively, providing insights into bone metabolism, adipose tissue, obesity and diabetes, and skeletal stem cells. Tables and figures are used to help the reader understand complex topics. The introduction is followed by specifically stating the hypothesis and aims of the study. The results are presented in the two already published papers, both as first author in two highly-ranked scientific journals, which further attests to the high quality of her work. Additional data are provided in the supplement. The discussion is well-rounded and puts the data into context of the current literature. The thesis is concluded with a summary of the results and an outlook that provides suggestions for new avenues for research. Overall, the thesis is easy to read and very informative.

An der Einfahrt Fiedlerstraße steht unser Parkhaus mit 500 Stellplätzen zur Verfügung.
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Specific questions to the author:

1. In the chapter 1.1.3., several factors are mentioned that regulate bone remodeling. However, aging and inflammation as two important regulators are not mentioned. Can the author elaborate on the effects of those factors on bone remodeling?
2. It is not fully clear why the factors chosen in table 1 were chosen. There are surely more pathways that regulate adipogenesis, for example, or more enzymes that participate in the regulation of osteoblasts and adipocytes. Can the author explain the selection of these factors?
3. In mice, a HFD leading to obesity is associated with reduced bone mass. How is the situation in humans? Are obese individuals protected from fractures, or not?
4. Did you investigate the effects of PUFA treatment on cBMAT and rBMAT?
5. Why do you think is osteoclastogenesis from cells from obese mice increased? Is it a direct effect or indirect via stromal cells?
6. How do you think does PUFA treatment relate to anti-oxidative treatment? Would they both have the same effects or what effects are specific to PUFAs and which to anti-oxidants (e.g. vitamin E)?
7. Since senescence markers were increased in HFD, would you plan to do senolytic treatments next?
8. Why did bone strength tend to be higher in the Pio group (or also, why was it not lower in the HFD group)?
9. You mentioned that C57BL6/N mice may result in different outcomes than using C57BL6/J mice – can you elaborate on the differences between these two strains?
10. Besides glutamine, also other amino acids have been shown to be important for bone and collagen production (e.g. L-arginine). Have you also seen other promising amino acids that may be worth following up in the future?

General note: differences in males and females should be regarded as sex-specific in animals, and not gender-specific.

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Taken together, Mgr. Benova submitted an excellent thesis on an important research topic. Her data provide novel insights into existing literature showing that dietary supplements and pharmacological strategies are valid to improve bone health under obese/diabetic conditions. She has applied a broad spectrum of methods including mouse experiments and cell metabolic studies. The fact that her results were already published in two high-ranked journals highlights the quality of her work.

Mgr. Benova clearly demonstrated the ability to work scientifically independently and creatively. Thus, I recommend this thesis to be approved and defended without reservations.

I confirm that I have no conflict of interest in relation to the author of the work.

Dresden, 12.06.2024

A handwritten signature in blue ink, consisting of a large, stylized 'R' followed by a horizontal line and a small 'n'.

Prof. Dr. Martina Rauner