

Contents

Preface.....	4
Acknowledgements.....	5
Abbreviations.....	7
Included articles.....	8
English Abstract.....	9
Dansk resumé.....	10
Introduction.....	12
Background.....	14
Bone biology.....	14
Composition of bone.....	15
Bone modeling and remodeling.....	16
Mechanical impact on bone.....	17
The Mechanostat theory.....	18
The Mechanostat related to osteoporosis.....	19
Mechanotransduction.....	21
Osteogenic exercise.....	23
High- and odd-impact exercise.....	24
Resistance Training.....	27
Assessment of osteogenic response to exercise.....	28
DXA Scan.....	29
Biochemical bone turnover markers.....	33
How to standardize the use of BTM when evaluating the osteogenic exercise.....	34
PINP.....	36
Osteocalcin.....	37
CTX.....	39
Literature review: BTM response to acute exercise and training.....	40
Timing of blood sampling in the reviewed studies.....	46
Acute BTM response to exercise.....	46
Longitudinal BTM response to training.....	52
Fracture risk assessment (FRAX).....	60
Material and methods.....	62

THE OSTEOGENIC STIMULUS OF EXERCISE
Bone health and osteoporosis risk assessment in women

Experimental designs	62
Participants	63
Exercise and training	64
Data analysis and statistics	67
Statistical power analysis.....	69
Results	73
Bone turnover marker response to exercise and training	73
Association between BTM and GRF	76
The effect of multimodal exercise training on bone mass and strength in postmenopausal women	76
The importance of including the measurement of BMD in FRAX for EBC women	78
Discussions.....	80
Summary and Conclusions.....	85
References	88
APPENDIX A – Included articles	100
STUDY 1	101
STUDY 2 (draft)	110
STUDY 3	130
APPENDIX B – Tables from the literature review on bone turnover markers	138

Included articles

STUDY 1, a randomized controlled cross-over design study

Acute Response of Biochemical Bone Turnover Markers and the Associated Ground Reaction Forces to High-impact Exercise in Postmenopausal Women

Rizky Suganda Prawiradilaga, Anders Odderup Madsen, Niklas Rye Jørgensen, and Eva Wulff Helge

Biology of Sport. 2020; 37(1):41–48

STUDY 2, an evaluation study

An Evaluation of Training in a Local Community Aimed at Musculoskeletal Health Promotion

Rizky Suganda Prawiradilaga, Magnus Bendtsen, Simon Esrup, and Eva Wulff Helge

(draft)

STUDY 3, an observational study

FRAX Calculated without BMD Resulting in a Higher Fracture Risk Than That Calculated with BMD in Women with Early Breast Cancer

Rizky Suganda Prawiradilaga, Victoria Gunmalm, Trine Lund-Jacobsen, Eva Wulff Helge, Charlotte Brøns, Michael Andersson, and Peter Schwarz

Journal of Osteoporosis – Volume 2018, Article ID 4636028, 6 pages

In addition, a preliminary literature review is included in this thesis (pp 40–60 and Appendix B)

Response of biochemical bone turnover markers to exercise and training

English Abstract

The primary aim of the present Ph.D. thesis was to investigate the osteogenic stimulus of acute exercise and longitudinal training for postmenopausal women and to contribute to the development of knowledge-based training recommendations for the prevention of bone loss and related bone fractures. A secondary aim was to investigate the impact of including bone mineral density (BMD) in the calculation of future fracture risk by the FRAX instrument. The thesis encompasses three human studies: One randomized controlled crossover study, one evaluation study and one observational study. In addition, a preliminary literature review of the response of biochemical bone turnover markers (BTM) to exercise and training is a part of the thesis.

It was evident from *the preliminary literature review* that the overall usage of BTM in exercise studies was characterized by a large variation in standardization of the method, which makes the comparison between different interventions and different populations very difficult. It is therefore highly warranted that future studies follow the recommendations of the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) and the International Osteoporosis Foundation (IOF).

The randomized, controlled crossover study investigated the acute response of BTM to three high-impact jumps, and a highly significant association between the three-dimensional ground reaction forces (GRF) produced by jumping and the acute BTM response was reported. It was concluded that high-impact jumping had an acute osteogenic impact on bone turnover with no difference between the three different jumps that were compared. Based on the results, inclusion of movements in various directions (odd-impact exercise) and multimodal training was recommended when planning osteogenic training programs.

The evaluation study investigated the longitudinal osteogenic impact of a health promotional training initiative in a local community over nineteen weeks. Despite the fact that the training was based on current theories on osteogenic training principles, the osteogenic effect was sparse, no matter whether it was evaluated by assessment of BMD or BTM. However, the multimodal training program had health enhancing effects on body composition and bone mass, together with a single increase in femoral trochanter BMD. It was hypothesized that the finding of limited osteogenic effect was partly

due to a suboptimal study design with a relatively low statistical power and an inadequate control of the individual training intensity, frequency, and volume.

The observational study investigated the relevance of including BMD in reliable fracture risk assessment (FRAX) for women diagnosed with early non-metastatic breast cancer. It was reported that when BMD was included in the calculation, the number of high-risk FRAX scores of hip fracture and major osteoporotic fractures were significantly lower ($p < 0.001$), while the number of low-risk FRAX scores were significantly higher ($p < 0.001$). Thus, it was concluded that when calculating the 10-year probability of hip fracture or major osteoporotic fractures in these patients it is important to include BMD to avoid overestimation of the fracture risk and thus, a possible overtreatment of the patient.

Dansk resumé

Det primære formål med denne ph.d. afhandling var at undersøge den osteogene stimulus af akut fysisk aktivitet og længerevarende træning for postmenopausale kvinder samt på længere sigt at bidrage til udviklingen af vidensbaserede træningsanbefalinger til forebyggelse af knogletab og relaterede knoglefrakturer. Et sekundært formål var at undersøge betydningen af at inkludere knoglemineraltæthed (BMD) i beregningen af fremtidig brudrisiko ved hjælp af FRAX-metoden. Afhandlingen omfatter tre humane studier: Et randomiseret kontrolleret crossover-studie, et evalueringsstudie og et observationsstudie. Derudover indgår et præliminært review af det biokemiske respons i knoglemarkører (BTM) ved hhv. akut fysisk aktivitet og træning.

Det præliminære review viste, at anvendelsen af BTM i studier af akut fysisk aktivitet og træning generelt var kendetegnet ved en stor variation i standardisering af metoden, hvilket gør sammenligning af forskellige interventioner og forskellige populationer meget vanskelig. Det er derfor stærkt påkrævet, at fremtidige studier, hvor BTM anvendes som markører for osteogen adaptation, følger anbefalingerne fra the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) og the International Osteoporosis Foundation (IOF).

Det randomiserede, kontrollerede crossover-studie undersøgte det akutte respons i BTM efter tre typer hop med høj impact og fandt en signifikant sammenhæng mellem de tredimensionelle reaktionskræfter fra underlaget (GRF) og det akutte BTM-respons. Det kunne konkluderes, at hop med høj impact havde en akut osteogen effekt på knogleomsætningen, og at der ikke var nogen forskel mellem de tre forskellige hop, der blev sammenlignet. Baseret på resultaterne blev anvendelse af aktiviteter med varierede bevægelser i forskellige retninger (odd-impact) og multimodal træning anbefalet, når man tilrettelægger osteogene træningsprogrammer.

Evalueringstudiet undersøgte den longitudinale osteogene effekt af et sundhedsfremmende træningstiltag i et lokalsamfund over 19 uger. På trods af at træningen var baseret på de gældende teorier om osteogene træningsprincipper, var den osteogene effekt sparsom, uanset om den blev evalueret ved hjælp af BMD eller BTM. Det multimodale træningsprogram havde imidlertid sundhedsfremmende effekter på kropssammensætning og knoglemasse og i tillæg dertil en enkelt stigning i femoral trochanter BMD. Det blev antaget, at fundet af begrænset osteogen effekt delvis skyldtes et suboptimalt studiedesign med en relativt lav statistisk styrke og en utilstrækkelig kontrol af den individuelle træningsintensitet, frekvens og volumen.

Observationsstudiet undersøgte relevansen af at inkludere BMD i en pålidelig vurdering af frakturrisiko (FRAX) hos kvinder, der er diagnosticeret med tidlig ikke-metastatisk brystkræft. Det blev rapporteret, at når BMD var inkluderet i beregningen, var antallet af høj-risiko FRAX-scorer for hoftefraktur og større osteoporotiske frakturer signifikant lavere ($p < 0,001$), mens antallet af lav-risiko FRAX-scorer var signifikant højere ($p < 0,001$). Det kunne derfor konkluderes, at når man beregner den 10-årige risiko for hoftefraktur eller større osteoporotiske frakturer hos disse patienter, er det afgørende at medtage BMD i beregningen for at undgå en overvurdering af frakturrisikoen og dermed en mulig overbehandling af patienten.

Introduction

Osteoporosis has become a major global concern for public health. It affects 200 million females globally and is estimated to cause over 8.9 million fractures annually [1]. This pathological condition is characterized by low bone mass and bone tissue microarchitectural damage, resulting in increased bone fragility and risk of fracture [2]. Decreases in bone mineral density (BMD) with age are, however, inevitable and physiological [3].

A possible way of preventing osteoporosis can be through engaging in evidence-based training to improve BMD and reduce age-related bone loss [4]. A meta-analysis study by Marques et al. [5] based on 19 randomized controlled studies (RCTs) have shown that exercise training in older adults has positive effects on increasing BMD. However, the specific mechanism is still unclear, and through dual-energy X-ray absorptiometry (DXA) scanning, it takes several months to observe changes in BMD and bone mass as a result of osteogenic adaptation.

Besides the DXA scanning use, the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) and the International Osteoporosis Foundation (IOF) have recommended the use of biochemical bone turnover markers (BTM) for the assessment of fracture risk and monitoring therapy in clinical settings [6,7]. The BTM, procollagen type 1 amino-terminal propeptide (P1NP) and C-terminal telopeptide of type I collagen (CTX) are specifically recommended as reference markers of bone turnover. They could therefore be a promising assessment of osteogenic response, since the BTM reflect the ongoing bone turnover and the changes that may be induced by exercise training.

However, only few studies examined the effects of exercise on BTM for postmenopausal women, and the results are varied. Therefore, the present thesis aims to evaluate the bone turnover response to exercise and training in addition to the longitudinal BMD response for postmenopausal women. The ultimate aim is the recommendation for evidence-based exercises to be included in everyday routines and thus to impact the public health.

It is hypothesized that high-impact exercise will induce osteogenic changes in BTM associated with the produced ground reaction forces (GRF) (STUDY 1). It is also assumed that evidence-based multimodal training as health promotion will have an osteogenic effect on bone mass and

bone strength as well as bone turnover that may counteract bone loss in postmenopausal women (STUDY 2).

In a health promotion and preventive perspective, it is highly relevant to estimate future fracture risk, especially for individuals with increased risk of compromised bone strength. A well-known tool to do so and with which to support clinical decision making is the Fracture Risk Assessment Tool (FRAX) [8], which can be used with or without measurement of BMD included. In STUDY 3 the impact of including BMD in the estimation of fracture risk with FRAX is studied in a group of breast cancer patients. It is hypothesized that DXA-scanning is necessary prior to treatment initiation of early breast cancer (EBC) women to avoid overestimation of fracture risk, which can lead to overtreatment (STUDY 3).

Thesis aims

The overall aim of this thesis is to investigate the osteogenic stimulus of exercise and training in women with the goal of contributing to knowledge-based training recommendations for the prevention of bone loss and related bone fractures. This includes the following specific aims:

- 1) To investigate the response of BTM to exercise (countermovement jump, drop jump, diagonal drop jump) and to training (19 weeks of multimodal training) in postmenopausal women (STUDY 1 and STUDY 2).
- 2) To evaluate the association between GRF and the acute BTM response (STUDY 1).
- 3) To evaluate the effect of 19 weeks of multimodal high-impact training in a local community aimed upon improving musculoskeletal health in postmenopausal women (STUDY 2).
- 4) To investigate the relevance of including the measurement of BMD in reliable fracture risk assessment for women diagnosed with early nonmetastatic breast cancer (STUDY 3).