Universität Basel

Research Project

Dose-response relationship of in vivo ambulatory load and cartilage biomarkers: the role of age, tissue health and inflammation

Third-party funded project

Project title Dose-response relationship of in vivo ambulatory load and cartilage biomarkers: the role of age, tissue health and inflammation
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Project start 01.01.2020
Probable end 31.12.2023
Status Active

Articular cartilage is an avascular and aneural tissue that facilitates joint motion with minimal friction. Osteoarthritis (OA) is a joint disease that affects the whole joint resulting in severe articular cartilage degeneration with a prevalence worldwide of more than 10%. Although the molecular mechanisms that trigger the pathological changes in OA are largely unknown, the ability of chondrocytes to respond to load is believed to play a critical role in maintaining healthy tissue and in the initiation of OA. Different modes of ambulation have resulted in increases of specific blood markers, and immobilization during bed-rest lead to reductions in the same blood markers. However, the dose-response relationship between ambulatory load and mechanosensitive blood markers, its biological variation in healthy persons and in patients with a high risk of developing OA (e.g. with increasing age or after joint injury), and its relevance for cartilage degeneration are unknown. Based on reported differences in the magnitude of load-induced changes in blood markers of articular cartilage depending on the type of physical activity, we have previously tested an experimental framework of a systematic and controlled modulation of weight bearing during a walking stress test that we propose to employ in this study. We will address the following specific aims:

Specific Aim 1: Investigate the in vivo dose-response relationship between ambulatory load and mechanosensitive blood markers of articular cartilage using controlled weight bearing during a walking stress test and age, tissue status and the presence of inflammation as experimental paradigms.
Specific Aim 2: Investigate the prognostic ability of the individual in vivo dose-response relationship between ambulatory load and mechanosensitive blood markers of articular cartilage for articular cartilage degeneration.

Healthy subjects and subjects with previous anterior cruciate ligament (ACL) injury aged 20 to 50 years will be clinically assessed, undergo magnetic resonance imaging (MRI) of both knees, and complete questionnaires on physical function and physical activity. Participants will wear an activity monitor for the 7 days before and during the experiment to record their physical activity level. Each participant will complete three walking stress tests (30 minutes walking) on separate days with repeated blood sampling to assess load-induced changes in levels of mechanosensitive blood markers (COMP, MMP-3, PRG-4, ADAMTS-4). In each test, one of three different ambulatory loads will be applied (80, 100 and 120% body weight (BW)). Inflammation will be assessed as IL-6 serum concentration. Tissue status of articular knee cartilage will be assessed as MRI T2 relaxation time and cartilage thickness at baseline and at 24-month follow-up.

This study can be considered as proof-of-concept of a potential diagnostic test (walking stress test) for cartilage mechanosensitivity and will provide first evidence of the role of age, tissue status and presence of inflammation on the dose-response relationship between in vivo ambulatory load and mechanosensitive blood markers of articular cartilage and its relevance for prognosing cartilage degeneration. These results will allow to judge the importance of mechanosensitive blood markers for in vivo mechanobiology of articular cartilage. The results of this study will reveal if the proposed experimental framework may be suitable in the area of cartilage engineering and transplantation and for testing pharmacologic agents and load-modifying interventions aimed at changing tissue metabolism in the context of OA pathomechanics that can be further investigated in ex vivo, in situ and in animal models of OA.

Financed by
Swiss National Science Foundation (SNSF)

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ID	Kreditinhaber	Kooperationspartner	Institution	Laufzeit - von	Laufzeit - bis
4508181	Mündermann, Annegret	Hirschmann, Anna, Advisor Radiology	University Hospital basel	01.01.2020	31.12.2023
4508182	Mündermann, Annegret	Liphardt, Anna-Maria, Advisor biomarkers	Universitätsklinikum Erlangen	01.01.2016	31.12.2023