Clinic for Orthopaedics and Traumatology

University of Basel Department of Biomedical Engineering

Universitätsklinikum Erlangen

Universitätsspital Basel

DOSE-RESPONSE RELATIONSHIP OF AMBULATORY LOAD AND MECHANOSENSITIVE CARTILAGE BIOMARKERS – EXPERIMENTAL FRAMEWORK

Simon Herger[1,2], Corina Nüesch[1,2], Anna-Maria Liphardt[3], Felix Eckstein[4], Christian Egloff[1], Annegret Mündermann[1,2]
[1]University Hospital Basel, Basel, Switzerland, [2]University of Basel, Basel, Switzerland, [3]Universitätsklinikum Erlangen, Erlangen, Germany,
[4]Paracelsus Medical University, Salzburg, Austria *Contact: simon.herger@usb.ch

Introduction

- Blood biomarkers have been used as surrogate parameters of cartilage metabolism and its degeneration.
- These markers have been found to be altered in subjects with OA [1] , and temporarily after cyclic exercise [2].
- Resting biomarker [3] levels and their changes after weight bearing exercise may predict future cartilage degeneration [4].
- The role of age, sex, injury and tissue status in the dose-response relationship between ambulatory load magnitude and blood marker kinetics is poorly understood.

Objectives

1. Is there biological variation in the dose-response relationship between ambulatory load and mechanosensitive cartilage blood markers concentrations, and to which degree can these be explained by age, tissue status or the presence of inflammation?
2. Does the individual dose-response relationship between ambulatory load and mechanosensitive cartilage blood markers predict future cartilage degeneration in persons at risk for developing early OA?

Methods

- 96 subjects in 4 subgroups of n=24 per group
  - healthy participants: 20-30 and 40-60 years
  - 2-10 year after ACL injury: 20-30 and 40-60 years
- Prospective experimental multimodal study, block randomization and crossover
- 30-minute walking stress test: 20% reduced, normal and 20% increased bodyweight (BW)
- Blood samples before and after walking stress test (Fig. 1)
- Spatiotemporal parameters, sagittal kinematics, vertical ground reaction force (vGRF)

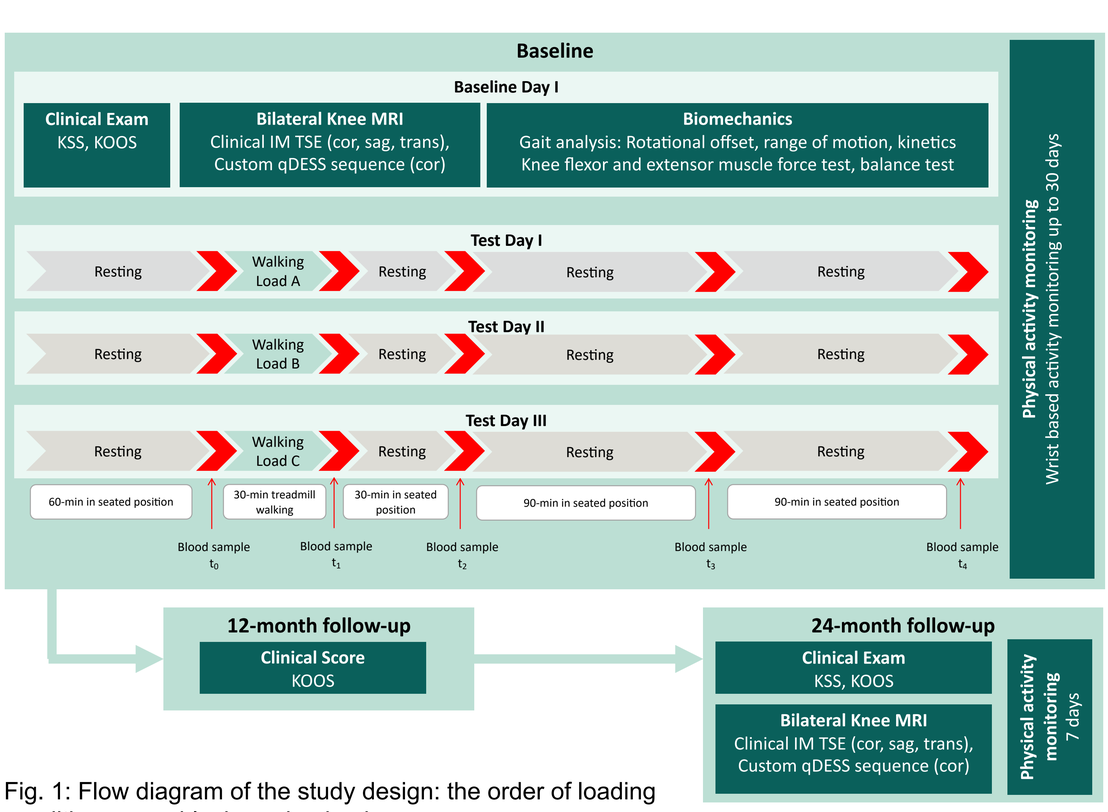

Fig. 1: Flow diagram of the study design: the order of loading conditions were block randomized.

- Serum sample concentrations measured using ELISAs and normalized to baseline concentrations (t_0)
- Articular cartilage of weight bearing tibiofemoral regions assessed using WORMS, and cartilage thickness and T2 relaxation (Chondrometrics GmbH)
- Mixed model calculations:
  - Changes in cartilage thickness and T2 relaxation time from baseline to 2-year follow up
  - Their association with load-induced changes in biomarker concentrations at baseline
  - Differences between age groups and ACL status

Where we are at the moment

- 31 subjects with completed baseline data collection
- Test images of qDESS have been obtained and quality controlled

Results

- Pilot study (n=24):
  - Reduced load: mean relative reduction in vGRF of -19.5% BW (Figs. 2, 3)
  - Increased load: mean relative increase in vGRF of +16.8% BW (Figs. 2, 3)
  - No relevant differences in spatiotemporal parameters and joint kinematics between loading conditions
  - Load-dependent changes in blood biomarker kinetics

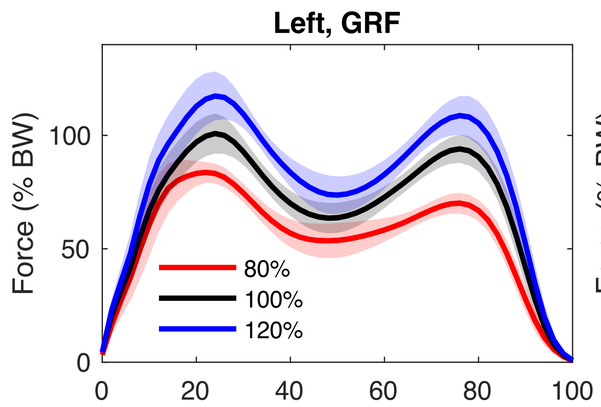

Fig. 2: mean (±1SD) ground reaction force (GRF) normalized to stand phase for **20% increased (80% BW)**, normal (black) and **20% reduced (100% BW)** bodyweight.

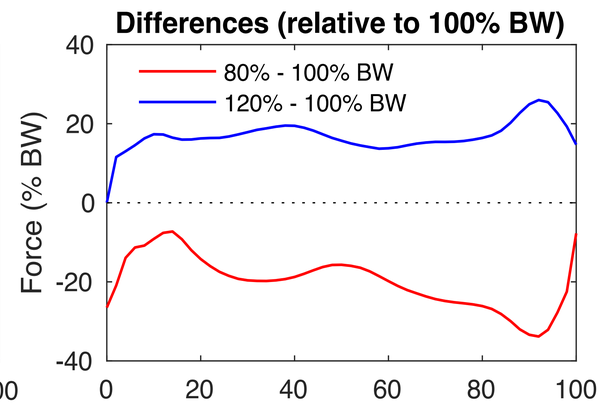

Fig. 3: Relative mean differences to normal bodyweight (BW).

Conclusions

We consider the combination of repeated MRI, biomechanical analysis, and cartilage serum biomarker analysis after walking with altered ambulatory load as an effective approach to extend current knowledge on serum biomarker metabolism and its association with future cartilage degradation.

References

[1] Clark, A. G., et al. (1999) *Arthritis Rheum.* DOI: 10.1002/1529-0131(199911)42:11<2356; [2] Roberts et al. (2019) *Eur. J. Appl. Physiol.* DOI: 10.1007/s00421-019-04232-4; [3] Kraus, V. B., et al. (2017) *Ann. Rheum. Dis.* DOI: 10.1136/annrheumdis-2016-209252; [4] Erhart-Hledik, J. C., et al. (2012) *Osteoarthr. Cartil.* DOI: 10.1016/j.joca.2012.07.018

Funding

SNSF 320030_184912, PI Mündermann.