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Effects of progressive resistance exercise on inflammatory processes in breast cancer patients undergoing radiation treatment

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The cancer-related fatigue syndrome (CRF) is one of the most frequently occurring side effects of cancer treatments during radiotherapy. Still, its pathophysiology is not well understood, and there exists no effective medical treatment. However, various exercise interventions have shown benefits on fatigue, including a progressive resistance training during radiotherapy that yielded significant improvements with respect to the physical dimension of fatigue in the randomized controlled BEST-Study. As some evidence exists that breast cancer patients undergoing radiation therapy exhibit increased levels of inflammatory parameters, and some studies have shown that exercise acts anti-inflammatory, the mode of action of exercise on inflammation and subsequently CRF is matter of ongoing investigations. Therefore, the aim of this dissertation project was to investigate within the BEST-Study the effect of progressive resistance training on inflammatory processes in breast cancer patients undergoing radiation treatment, and to evaluate the role of inflammatory processes regarding the intervention effect on the physical dimension of CRF.

Specific objectives were (1) to measure inflammatory parameters (IL-6 and IL-1ra) in serum of the breast cancer patients who participated in the BEST-Study, (2) to analyse baseline determinants of these inflammatory markers, (3) to investigate the exercise intervention effect on inflammation, (4) to investigate the association with physical fatigue and a potential mediating role of inflammation regarding the previously shown benefit of the resistance training on physical fatigue, and (5) to discuss the finding in light of the existing literature.

In the BEST-Study breast cancer patients undergoing radiotherapy were randomized into a resistance exercise group (n =80) or a muscle relaxation control group (n =80). Levels of IL-6 and IL-1ra in serum of these patients were assessed before the beginning of the intervention and radiation therapy (T0), at the end of the radiation therapy (T1) and at the end of the 12-week intervention (T2).

The results showed that current infection, higher waist-hip ratio (WHR) and body mass index (BMI) and respiratory disorders were significantly associated with higher IL-1ra concentrations at baseline. IL-6 on the contrary was only associated with higher WHR and age. In addition both interleukins displayed borderline significant associations with recently preceding chemotherapy treatment. Among controls, who had received preceding

chemotherapy the concentration levels in both cytokines decreased from initial high levels at baseline (T0) till the end of radiotherapy (T1).

Further, our study showed a significant exercise intervention effect on change in inflammatory markers from pre- to post-radiotherapy among patients without previous chemotherapy. In line with previous studies IL-6 levels increased during radiotherapy in the control group. This increase in inflammation appeared to be counteracted by the resistance exercise. IL-1ra however did not display any changes in concentration levels in the exercise group or in the relaxation group.

Regarding the relationship between inflammatory markers and cancer-related fatigue, our results showed significant associations between IL-6 and physical fatigue pre- and post-radiotherapy among chemotherapy-naïve patients. Results including patients with previous chemotherapy as well as the results regarding IL-1ra were less clear. Mediation analyses revealed that IL-6 partly mediated the beneficial effects of resistance exercise regarding physical fatigue during radiotherapy. The specific mechanism however needs to be further investigated, as the intervention effect could not fully be explained by this parameter.

In conclusion, this study suggests that the inflammatory marker IL-6 increases during radiotherapy, yet this increase might be counteracted by resistance exercise. IL-1ra on the contrary does not appear to increase from pre- to post-radiotherapy and no intervention effect and also no clear associations with fatigue were found. IL-6 was significantly associated with physical fatigue pre- and post-radiotherapy in the chemotherapy-naïve patients, and the beneficial effect of resistance exercise on physical fatigue appeared to be mediated by IL-6 to a certain extent. However, it seems to be not the sole molecular pathway for mediating this exercise effect.