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## **May bed rest cause greater muscle loss than limb immobilization?**

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Bed rest, as often occurs following surgery or during (critical) illness, may result in greater muscle loss than local muscle disuse; not only because of the amount of muscle tissue that is subjected to disuse, but also because of various systemic factors that may accelerate muscle atrophy. These factors could include hormonal changes or (low grade) systemic inflammation. In medical research, experimental (whole-body) bed rest and (local) limb immobilization are typically applied in healthy volunteers to investigate the impact of disuse on the loss of muscle mass and strength. Previous work, based on combined results of separate studies, has suggested that immobilization leads to more pronounced muscle loss than bed rest due to the greater degree of restriction imposed (Clark, 2009). However, a direct comparison of the loss of muscle mass and strength between both models is currently lacking.

To test the hypothesis that bed rest would lead to greater muscle loss when compared with single leg immobilization, we subjected twenty healthy, age- and BMI- matched males (age  $23 \pm 1$  y, BMI  $23.2 \pm 0.7$  kg·m<sup>-2</sup>) to either 7 days of leg immobilization via a full leg cast ( $n=10$ ), or 7 days of strict bed rest ( $n=10$ ). Here we present novel data showing that quadriceps cross-sectional area (CSA), as a measure of skeletal muscle mass, declines during 7 days of disuse in both models ( $P < 0.001$ ), with no differences observed between the immobilised leg (from  $7646 \pm 399$  to  $7229 \pm 373$  mm<sup>2</sup>) and the leg(s) in the bed rest model (from  $7900 \pm 315$  to  $7664 \pm 354$  mm<sup>2</sup>;  $P > 0.05$  for *time x treatment* interaction). These declines in quadriceps CSA represent  $5.4 \pm 1.0$  and  $3.2 \pm 0.9\%$  leg muscle atrophy following leg immobilization and bed rest, respectively (**Figure 1**). Muscle atrophy during disuse was accompanied by a mean  $7 \pm 2\%$  decline in maximal leg strength ( $P < 0.01$ , measured as one-repetition maximum (1RM)), which also did not differ between the two models ( $6 \pm 3$  vs  $8 \pm 2\%$  following leg immobilization and bed rest, respectively;  $P > 0.05$ ).

In contrast with previously published data (Clark, 2009) and contrary to our hypothesis, we report an equivalent decline in leg muscle mass following short-term muscle disuse in both models. Irrespective of the model, we show that seven days of disuse leads to  $\sim 0.6\%$  leg muscle loss per day. These data are in line with previous work showing an approximate  $0.5-0.7\%$  muscle loss per day during muscle

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disuse (as reviewed in (Wall and van Loon, 2013)). By way of comparison, the ~140 g loss of leg muscle tissue (representing 3.2% of quadriceps CSA loss) measured via DEXA following bed rest translates to ~220 g leg muscle loss (representing 5.4% of quadriceps CSA loss) following leg immobilization. However, due to the involvement of the entire body during bed rest, more muscle tissue was lost following bed rest. The ~1.4 kg lean tissue loss following one week of bed rest includes muscle loss in both legs as well as in the upper body (LeBlanc et al., 1992), and by far exceeds the muscle loss observed in a single leg (~220 g) following one week of leg immobilization.

Theoretically, systemic changes associated with whole-body disuse may result in a greater degree of muscle loss following bed rest when compared with limb immobilization. Such factors could include inflammation (Jurdana et al., 2015), whole-body insulin resistance (Stuart et al., 1988), or increased stress hormone levels (Ferrando et al., 1999). However, our direct comparison shows no differences in the loss of leg muscle mass or leg strength following single leg immobilization and whole-body bed rest. Therefore, in healthy volunteers there do not seem to be any relevant systemic factors that further accelerate muscle loss in a model of short-term bed rest compared with limb immobilization. Obviously, the decline in cardiac output (Saltin et al., 1968), tissue perfusion (Broderick et al., 2009), and whole-body and peripheral insulin sensitivity (Stuart et al., 1988) observed following (short-term) bed rest do not seem to accelerate the loss of leg muscle mass or strength.

From an experimental point of view, it could be argued that mechanistic studies aimed at understanding disuse atrophy may be better suited to implement a limb immobilization model to isolate the effect of disuse on muscle tissue *per se*. In contrast, the bed rest model offers a more relevant model from a clinical perspective as it represents a period of hospitalization and its implications, including changes in organ and tissue function.

Short-term muscle disuse following leg immobilization and bed rest leads to substantial declines in skeletal muscle mass and strength. Although leg muscle atrophy does not differ between both models of disuse, whole-body lean mass loss is, of course, greater following bed rest compared with single leg immobilization.

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**Disclosure summary:** The authors have nothing to declare.

## Author contributions

MLD, BTW, and LJCvL designed the study. MLD, EMPB, and BTW organized and performed the experiments. MLD performed the analyses and analysed the data. MLD, EMPB, BTW, LBV, and LJCvL interpreted the data. MLD drafted the manuscript. MLD, EMPB, BTW, LBV, and LJCvL edited and revised the manuscript, and approved the final version.

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**Figure legend**

**Figure 1:** Loss of leg lean mass and total lean mass following 7 days of muscle disuse in a model of leg immobilization versus bed rest. Data on leg lean mass following leg immobilization are extrapolated from muscle loss measured via quadriceps cross-sectional area (CSA;  $5.4 \pm 1.0$  and  $3.2 \pm 0.9\%$  decline in quadriceps CSA following 7 days of leg immobilization and bed rest, respectively) and DEXA scans made following 7 days of bed rest.

**Figure 1**

