Valorization

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Relevance

Hospitalization, often required during illness or following surgery, is associated with high health care costs. To illustrate this, the costs for one hospital bed per day in the Netherlands is 200 euro (based on primary, secondary and tertiary hospitals, [1]). At present, individuals who are admitted to the hospital have an average length of stay of less than 7 days [2]. During such periods of muscle disuse, patients suffer from muscle loss, which has been shown to be predictive of mortality [3]. Periods of hospitalization have been shown to be of particular relevance to the elderly population. Currently, the length of hospital stay has been demonstrated to increase with advancing age from the age of 40 [2]. Periods of muscle disuse not only occur during hospital admission, but also when an individual is struck with illness at home. While younger individuals demonstrate a full natural recovery after a period of disuse, recovery from disuse in elderly has been shown to be impaired [4]. More specifically, a 4-week progressive resistance-type exercise program was insufficient to fully regain lost muscle mass in the elderly [4]. The accumulation of such short periods of muscle disuse has been thought to contribute to the loss of muscle mass and strength with ageing, termed sarcopenia [5, 6]. Due to the greater longevity, the subpopulation of elderly individuals aged 80 year and older is currently the fastest growing subpopulation in the developed world [7]. In the Netherlands, it has been estimated that in 2040 the number of people aged 65 and over will have increased to 4.8 million [8]. Together with the fact that life expectancy keeps on increasing [8], there will be more elderly people who are at risk for the negative consequences of muscle disuse in the next decades.

Nowadays, the Netherlands have more day care patients than in-patients [2], which demonstrates that we are able to minimize hospital stay. Moreover, in-patients are dismissed earlier, which is demonstrated by a reduction in average hospital length of stay from 7.5 days in 2003 to 5.2 days in 2013 [2]. However, a possible hazard could be that in the eyes of our physicians and health care workers, it is no longer worth to focus on preventing muscle loss during this decreased length of stay.

Target groups

In the present thesis, we have investigated strategies to combat muscle atrophy during short-term muscle disuse in a controlled laboratory setting. Even though within the scientific community there is consensus that merely a few days of muscle disuse already leads to various negative health consequences, our findings have not yet been translated to the general public. Firstly, amongst patients awareness should be created of the impact of even short-term muscle disuse. Obviously, it should be emphasized that such periods should be avoided or shortened as much as possible. It is the task of physicians and health care workers to educate patients in this. During hospital stay, patients are

currently not encouraged to be active: their food is served at the bed side and an appointment with their physician takes places in the patients' room. As a result, elderly hospitalized patients spend 83% of their entire time in bed [9]. Of their time out of bed, they spend a mere 43 minutes per day standing or walking [9]. There is a clear role for policy makers here, as the mindset and logistics in hospitals need to be altered to change the current situation. Examples of minimizing physical inactivity in hospitals could entail serving meals in a shared dining room, assuring that patients visit their physician in her/his consulting room, and implementing digital (e.g. via television or internet) or real life physical activity or exercise (e.g. guided by a physical therapist). In order to achieve this, policy makers have to provide financial and (infra)structural support. Lastly, in the future insurance companies can benefit from the beneficial effects of NMES, applied with or without (more) protein rich nutrition. However, they will likely wait with implementing such a technique until the long-term effects are demonstrated in a large multicentre trial.

The results of this thesis are of great relevance for people who undergo a (short) period of disuse, and consequently lose a substantial amount of muscle mass. Muscle disuse is associated with specific type II muscle fibre atrophy [10]. Such fibre-type specific atrophy is not only seen in situations of muscle disuse, but also occurs in patients with cancer cachexia and chronic obstructive pulmonary disease. There is limited knowledge on the efficacy of NMES and protein ingestion in these patient groups. However, based on the results of this thesis, these interventional strategies are promising to have a beneficial effect in other situations of selective type II muscle fibre atrophy.

Products and activities

The current thesis demonstrates the efficacy of NMES to evoke muscle contractions and prevent muscle disuse atrophy. However, NMES is not a new technique: already in 1987 its value was demonstrated in a patient cohort by Gibson and co-workers [11]. The studies in the present thesis have advanced our knowledge on the applicability of NMES by confirming its efficacy during short-term disuse in healthy individuals (Chapter 4) and comatose patients (Chapter 5). Moreover, we have applied NMES in combination with nutritional intake (Chapter 7 and 8) to optimize the treatment of patients undergoing a period of disuse. Future large, multicentre trials should be conducted to assess the long-term impact of NMES. Obviously, it is important to focus on outcomes such as hospital length of stay, morbidity, and mortality rates in such large clinical trials. Additionally, it is relevant to also assess the long-term effect of NMES during hospitalization (e.g. 1-year following hospital discharge) on muscle function, metabolic health, and quality of life. In parallel, NMES can theoretically be safely used by individuals who undergo a period of muscle disuse. However, before NMES can be used in an unsupervised manner, technological developments are necessary to improve user friendliness. Devices should be able to adjust the stimulation intensity based on feedback on the extent of

muscle contraction, so that throughout the session a full muscle contraction can be guaranteed without any input from the user. Currently, NMES devices are not yet able to perform in this way. This implies that if hospitals want to introduce the technique as it stands now, all sessions will have to be guided by a physical therapist or nurse. Given the time commitment of the procedure, this will decrease the cost-effectiveness. It is therefore necessary to re-design these devices.

As part of this thesis we tested the efficacy of protein supplementation to attenuate muscle atrophy during short-term immobilization in elderly volunteers (Chapter 6). There we showed that twice-daily protein supplementation did not affect muscle atrophy, suggesting protein supplementation is not of additional value when an individual's habitual protein intake is maintained at a sufficient level. This is line with previous work, which suggested that protein supplementation is of surplus value in individuals consuming no more than 0.8 g per kg bodyweight per day [12], which is the current Recommended Dietary Allowance (RDA) for protein intake. Nutrition companies should continue their work in optimizing food products that are suitable for stimulating muscle protein synthesis and thereby minimizing muscle loss in undernourished patients. It is crucial that food intake is monitored thoroughly at hospital admission and during hospital stay, in order to tailor dietary intake plans to individual patient's needs. In healthy individuals, it is possible that not total daily intake, but distribution of intake (i.e. feeding pattern) and type of protein are more important. More knowledge on the effect of dietary feeding pattern and type of protein on muscle atrophy is necessary to develop more specific clinical nutrition products.

Personal perspective

Throughout the years of my PhD trajectory, it became clear to me that scientists tend to focus on a small topic while sometimes losing overview of the other processes that are possibly implicated. In muscle disuse research, many advances in the field of muscle protein metabolism have been made over the past years. However, as demonstrated in Chapter 10, muscle disuse not only leads to muscle atrophy but also leads to a disturbance in metabolic health, demonstrated by a marked reduction in insulin sensitivity. To date, there are few data available on the interaction between muscle disuse atrophy and the disuse-induced decline in metabolic health. I look forward to continue working on this topic in the future, to unravel the impact of muscle disuse on both muscle quantity and quality.

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