

Loss of muscle mass in hip fracture patients

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Valorisation

Relevance

The aged population is rapidly growing, and the number of people aged 65 years and older is expected to nearly triple by 2050, then representing 16 percent of the world's population ¹. In high-income countries such as the Netherlands, predictions show that even 33% of the population will be older than 60 years in 2050. These demographic shifts will have profound implications for our healthcare system. While infectious and acute disease are waning in Western societies, frailty and degenerative disease will emerge as more significant health problems. The increasing life expectancy thereby challenges society to maintain health and functional capacity in its older people. One of the age-related changes that strongly impacts on health and function is the gradual, progressive loss of skeletal muscle mass. Adults lose an average of 25% of their skeletal muscle mass between the age of 40 and 70 years, with an accelerated loss after the age of 70 years, although with individual variation. The co-occurrence of loss of muscle mass and decline in muscle function or strength is termed sarcopenia. Sarcopenia is a syndrome characterised by progressive and generalised loss of skeletal muscle mass and strength increasing the risk of frailty and predicting physical disability, loss of independence, poor quality of life, and death ². It is, therefore, considered an undesirable consequence of ageing with both personal and societal impact. From 2016, sarcopenia has been recognised as a disease entity and has been given an ICD-10-CM code (International Classification of Diseases, Clinical Modification). For these reasons it is of great importance to understand the various factors underlying sarcopenia and to develop effective interventions to prevent or delay the onset of sarcopenia.

The clinical relevance of sarcopenia is emphasised in elderly hip fracture patients. The decline in skeletal muscle mass and function predisposes to falls and fall-related fractures. The ability of skeletal muscle to generate an adequate amount of force is fundamental for balance and prevention of falling. Elderly suffering from sarcopenia, therefore, have a three times higher risk of falling, regardless of age and comorbidities ³. The total number of hip fracture patients is expected to further increase in the upcoming decades as a consequence of the demographic changes. The cost of care for hip fracture patients are about three times greater than age and residency-matched controls without a fracture. The personal proverbial costs of a hip fracture are also high, since hip fracture patients have an increased risk of mortality. Up to 30% of hip fracture patients does not survive the first year following the injury. Importantly, due to a decline in mobility and function, more than half of the patients

becomes unable of living independently. It is, therefore, not surprising that hip fracture patients experience lower quality of life than their age-matched controls.

This dissertation provides evidence that sarcopenia plays an aetiological role in suffering a hip fracture in the elderly. The loss of skeletal muscle mass with ageing can mainly be attributed to a reduced type II muscle fibre size, accounting for the majority of the loss of muscle mass ^{4,5}. Type II muscle fibres are essential for rapid muscle force production and are, therefore, essential in preventing falls. The work in this dissertation used percutaneous skeletal muscle biopsies of the *m. vastus lateralis* to assess muscle fibre characteristics of older hip fracture patients. We compared the muscle fibre characteristics of older hip fracture patients with age-matched controls without fall-related fractures in the medical history in one study, and compared muscle fibre characteristics between hospital admission and hospital discharge in another study. We demonstrate that older hip fracture patients suffer from sarcopenia at a muscle fibre level, showing extensive type II muscle fibre atrophy at time of hospital admission. Furthermore, we observed that older hip fracture patients even show signs of type I muscle fibre atrophy. We speculate that during hospital admission, older hip fracture patients suffer from on-going atrophy due to a combination of factors such as surgical intervention, pre-operative fasting, and physical inactivity. We observed substantial loss of skeletal muscle mass perioperatively during hospital admission, as measured with CT-scans to assess muscle cross-sectional areas of the upper legs. This emphasises the need for the development of effective interventional strategies to combat the loss of skeletal muscle mass in this compromised group of patients.

Healthcare implementation and products

Researchers nowadays have recognised the importance of sarcopenia as a prognostic indicator of post-operative outcome and discharge destination. Among hospitalised patients in general, sarcopenia seems to have the greatest prevalence at the orthopaedic trauma wards ⁶. The European Working Group on Sarcopenia in Older People recommends using the presence of both low muscle mass and low muscle function for the diagnosis of sarcopenia ². Evaluation of sarcopenia in hip fracture patients can be challenging due to mobility problems and pain, both pre- and postoperative. However, the clinical features of sarcopenia are obvious in most of the hip fracture patients. It can be seen as the 'elephant in the (operating) room': it is easy to spot, but often ignored. Currently, in most Dutch hospitals, the treatment of hip fractures has evolved into fast-track surgical programs. This multidisciplinary approach includes preoperative optimisation of cardiac function, electrolyte

disturbances, early surgery and early mobilisation, adequate analgesia, and thromboprophylaxis. The role of nutritional support can be integrated in these programs to target the on-going loss of skeletal muscle mass during hospitalisation. In pre-habilitation programs, which have been developed to prepare patients prior to hospitalisation and surgical treatment, the role of nutritional support is already more profound. Even though there is increasing awareness on the negative health consequences of hospitalisation in the older population, patients themselves are often unaware of the importance and relevance of nutrition and physical activity during their hospitalisation and subsequent recovery. Physicians, nutritionists, and physical therapists have a role to make patients aware that surgery and pharmaceuticals are not the only cornerstones of their treatment. In the ESPEN guidelines on clinical nutrition in surgery, integration of nutrition into the overall management of the patient, start of early nutritional therapy as soon as a nutritional risk becomes apparent, and early mobilisation to facilitate muscle and connective tissue protein synthesis and muscle function are recommended ⁷. Targeted interventions to combat the loss of skeletal muscle mass and strength during hospitalisation and rehabilitation after a hip fracture may contribute to better outcomes and quality of life in the older hip fracture patients. These principles can lead to development of specific products and innovations in the (clinical) nutrition industry.

Stimulation of the protein synthetic response to food intake is one of the principles in the development of nutritional interventions. Older hip fracture patients may need other anabolic stimuli from a nutritional product than healthy (young) patients, because of the concept of anabolic resistance ^{8,9}. The current dissertation explores nutritional strategies to stimulate muscle protein synthesis rates in healthy and sarcopenic older individuals. We explored basal muscle protein synthesis rates in sarcopenic older adults, which has never been done before. We demonstrated that ingestion of a nutritional supplement containing 21 gram of leucine-enriched whey protein is effective in stimulating muscle protein synthesis, and that this is not modulated by the addition of carbohydrates and fat to the product. This is an important finding given that nutritional supplements provided in the hospital setting often contain all macronutrients. The findings on muscle protein synthesis in the sarcopenic older patient are also encouraging. We were able to effectively stimulate muscle protein synthesis rates in sarcopenic patients by ingesting this leucine enriched whey protein. This proves that targeting muscle loss in sarcopenic elderly is possible despite their anabolic resistance. The presented data could be used for further nutritional product development. However, studying the acute effects of a nutritional intervention in a laboratory setting in sarcopenic elderly can still be

drastically different from the effect on muscle protein synthesis rates in sarcopenic hip fracture patients in a hospital setting. The optimal composition of a nutritional supplement for elderly hip fracture patients remains to be determined. Parts of this dissertation have been conducted within the framework of TIFN, a public-private partnership of universities and the nutritional industry, where research findings have been shared with industrial partners throughout the last years. This platform allows industries to implement scientific research into concept and product innovations and can help all partners solving more pieces of the puzzle. Combining knowledge will allow us to develop more effective intervention strategies to combat the devastating loss of muscle mass and/or strength in older hip fracture patients.

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