Skeletal muscle health in aging

IMPACT

What is the main objective of the thesis, and what are the most important results and conclusions?

Between 1990 and 2019, the number of people older than 80 has tripled, and this number is expected to triple again by 2050 (1). This enormous accomplishment of increasing life expectancy illustrates the remarkable advances achieved in biomedicine and healthcare but comes at a cost though, since many diseases such as type 2 diabetes and cardiovascular diseases are more prevalent at an older age (2). Moreover, in proportion, there are increasingly more older adults in the population than young individuals, an imbalance known as the 'silver tsunami,' which implicates increased healthcare costs and significant social challenges. If we consider the aging human body, skeletal muscle is prominently affected. Age-induced loss of lean muscle mass and function is known as sarcopenia and leads to disabilities and increased dependency and care needs. A better understanding of the aging process itself, rather than focusing on age-associated disease, can help to develop strategies to target the aging process and maintain people's health during those extra years of life.

In the cells of the human body, the mitochondria are organelles that maintain cellular energy levels necessary for all vital processes. As a result, mitochondria are also known as the cell's powerhouses. In muscle cells, healthy mitochondria regulate various metabolic processes and provide energy for muscle contractions. It is well documented that with aging, muscle mitochondrial function declines, which is paralleled by a loss in muscle strength and mass. Importantly, this reduction in muscle health translates into a loss of physical independence and an increased risk for metabolic disease. If and how age-related alterations in mitochondrial function and muscle health (causally) relate to each other is however not well established in humans. This thesis aimed to better understand the aging process in skeletal muscle by investigating the role of mitochondrial metabolism in the age-related loss of physical performance.

It has become increasingly clear that mitochondria do not operate as individual organelles but physically and functionally connect into dynamic networks. These networks are constantly built, restored, and subjected to quality control mechanisms

to assure efficient mitochondrial function. Growing evidence indicates that altered mitochondrial dynamics and impaired quality control influence skeletal muscle health in aging and metabolic disease. In **chapter 2** this evidence was reviewed in a literature study on the role of abnormal mitochondrial network dynamics in the age-related loss of muscle health. However, more - especially human - studies are needed to understand the implications and underlying mechanisms in order to develop new therapeutics to target mitochondrial dynamics in human disease. An important first step in this context is to develop suitable techniques to study these dynamic processes properly.

To better understand the relationship between skeletal muscle mitochondrial metabolism and muscle health, we, in **chapter 3**, extensively measured mitochondrial capacity and muscle function in young and older adults. We found that aging is associated with a decline in mitochondrial capacity, muscle health, and physical function. Interestingly, this decline was observed in older adults despite the fact that they performed more than 10000 steps-per-day, which is above the general physical activity recommendations. Since we also studied trained older adults in this study, we could also show that only a further increase in physical activity levels, achieved through regular high-intensity exercise training, was able to prevent the effects of aging on muscle health. Furthermore, we found a correlation between mitochondrial function and muscle health, indicating that maintaining mitochondrial function at older age is important to promote healthy aging.

To further understand why mitochondrial function declines when we age, we next studied the muscle tissue of the young and older participants and compared their metabolic profiles, using untargeted metabolomics (**chapter 4**). The most prominent change we observed was an age-related decline in NAD^+, an essential metabolite that is needed in the mitochondria to generate energy. Interestingly, this decline in NAD^+ was exacerbated in older individuals with a lower physical function and was nearly entirely prevented in the exercise-trained older adults. NAD^+ also strongly correlated to the average steps-per-day and mitochondrial and muscle functioning, demonstrating the importance of exercise to age healthier and suggesting a crucial role of NAD^+ therein.

A strategy to potentially alleviate the age-related depletion of NAD^+ in the mitochondria is by stimulating NAD^+ synthesis through nutritional supplementation of NAD^+ precursors. In this context, **chapter 5** explored the effectiveness of NAD^+ precursors supplementation (consisting of tryptophan, vitamin B3, and nicotinamide) on NAD^+ levels, mitochondrial function, and muscle health in older adults with reduced physical function. Nevertheless, the extra intake of these NAD^+ precursors appeared not to be sufficient to boost mitochondrial function and failed to improve physical function.

One of the most critical consequences of age-related decrease in physical function is the loss of balance control leading to an increased risk of falls and fall-related effects such as fractures, further functional decline, immobility, and causal mortality. Therefore, fall prevention therapy is essential to promote healthy aging. The reduction in muscle strength and mass is assumed to be the main reason for the age-related loss in the ability to cope with balance disturbances. Nevertheless, in **chapter 6**, no strong correlations were observed in young and older adults between muscle characteristics and balance control. These results indicate that fall prevention therapy in older individuals should not only focus on improving muscle quality, but a multi-domain intervention might be necessary.

Taken together, results from this dissertation indicate the importance of mitochondrial function and NAD^+ metabolism in muscle aging and suggest that physical exercise training remains the most powerful tool to improve mitochondrial function and to age in a healthy way. A better understanding of the role of NAD^+ in muscle metabolism and the mitochondrial quality control mechanism can reveal promising therapeutic targets to promote healthy aging**.**

What is the contribution of the research results to science and society?

The studies described in this thesis add to the existing knowledge on changes that occur in skeletal muscle while human age. With this new knowledge, we add some pieces to the puzzle and contribute to the clarification of the complex process of aging. Our results may help to identify new targets and approaches in order to prevent age-related disability and help people live a long healthy life.

Due to the vital role of skeletal muscle in daily life activities, the deterioration of muscle mass and function (sarcopenia) leads to a decreased quality of life, increased hospitalization rates and the loss of independence. Over the coming decades, the prevalence of sarcopenia is expected to increase drastically in Europe, and these trends will not only be a burden for the older population. They will impose a tremendous financial load on society as a whole in terms of increased healthcare costs, which are expected to double for European countries such as The Netherlands (3). To make healthcare affordable and preserve a good quality of life, it is crucial to maintain people's health and physical independence at older age. A better understanding of the aging process itself can help us identify strategies to promote healthy aging and significantly impact society.

To whom are the research results relevant?

The research results of this thesis are relevant to different stakeholders. First of all, these results are of interest to researchers working in the field of aging and aging-related diseases, as they contribute to a better understanding of how skeletal muscle metabolism and function change as we age. With this knowledge, researchers can investigate new targets and explore new avenues aimed at growing old in a healthy way. The new insights into the relationship between impaired muscle health and mitochondrial metabolism are also interesting to the food industry, as mitochondrial metabolism may be sensitive to nutritional intervention. This opens up new opportunities to develop nutritional strategies to prevent the age-related loss of physical function. The research results also support clear benefits of exercise training for older adults, which allow better recommendations, explanations, and motivations on how to maintain a healthy lifestyle. These recommendations can be adopted by the government and/or healthcare in general. Finally, these studies are of interest to the general public as they provide leads on how to preserve a healthy muscle function and a high quality of life while aging.

Several communication strategies are applied to inform the various relevant stakeholders. The results are used for original scientific articles which have been submitted to international, peer-reviewed journals. Once these articles are published, the knowledge from these studies is shared with scientists worldwide. The studies

have also been presented at several conferences and symposia, which increases the visibility of the results and thereby contributes to new insights and ideas for future research. In addition, during regular expert meetings and project-based seminars, the results have been shared regularly with the industrial partners and collaborating universities within the TIFN Mitochondrial Health project. Being part of this TIFN consortium enhanced collaborations between academia and industry, thereby fostering translational research. Finally, the results can be communicated during general lectures to increase public awareness of the importance of healthy aging

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