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CHAPTER 8

Perspectives

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This thesis aimed to describe the role of glucose metabolism in human longevity and to translate the results to an intervention aimed at improving health at older age in the general population.

General conclusions

In the first part, we found several indications for enhanced glucose metabolism in long-lived families. Middle-aged individuals predisposed to longevity were characterized by:

- enhanced insulin action at the level of the skeletal muscle
- lower accumulation of intramyocellular lipids
- lower nocturnal glucose levels

These results have provided the biological basis upon which health-promoting intervention in older age may be funded. In the second part, we have shown that:

- an internet-based intervention is effective at increasing physical activity and improving health in an older population
- increasing total daily physical activity in sedentary elderly leads to better metabolic health

Future directions

Although we have found multiple indications for the role of both insulin-dependent and insulin-independent enhancement of glucose metabolism in human longevity, the precise mechanisms behind these findings are not yet elucidated.

To explore the mechanisms of enhanced insulin sensitivity, further study should address the role of in vivo mitochondrial function in human longevity. The lower IMCL levels found in our study **(chapter 3)** may, in case of positive energy balance, be indicative of a lower need of fuel source for fatty acid oxidation, and hence, more efficient mitochondrial function (11) . Higher fatty acid levels and their derivatives in IMCL are thought to interfere with insulin signaling, and increased mitochondrial function could provide the explanatory mechanism between lower IMCL and resulting enhanced insulin sensitivity in the offspring of long-lived nonagenarian siblings. However, the reverse mechanism has also been proposed, where higher IMCL, as a consequence of dietary intake or low levels of physical activity, diffuse into mitochondria where they induce mitochondrial damage, thereby reducing mitochondrial capacity (5; 9). Future studies should therefore address 1. whether increased mitochondrial capacity is indeed present in long-lived families, and 2. whether lifestyle interventions, such as caloric restriction or increased physical activity might enhance mitochondrial function and insulin sensitivity.

Moreover, we surprisingly found indications of non-insulin dependent changes in glucose metabolism, as demonstrated by lower nocturnal glucose levels in offspring of nonagenarian siblings **(chapter 5)**. As continuous glucose monitoring has only recently become available for study of ambulant 24-hour glucose levels, and has scarcely been used for study in healthy populations, the mechanisms behind this finding are of speculative nature. Potential mechanisms include changes in the central regulation of glucose levels. For instance, both the autonomic nervous system and hypothalamic-pituitary-adrenal axis may modulate the nocturnal hormonal responses of growth-hormone and cortisol, thereby altering the rate of glucose utilization and production during the night (2; 6; 8; 10). Future study should combine 24-hour glucose measurements with circadian rhythms of GH and cortisol, and measures of (para)sympathetic nervous system activity, to study these pathways in long-lived families.

In the second part of this thesis, we described the effectiveness of an internet-based intervention at increasing physical activity and improving metabolic health in a sedentary older population **(chapter 6 and 7)**. These results are promising in light of the current lack of large-scaled preventive programs directed at lifestyle change in older populations. With internet as potential medium for delivering low-cost and accessible interventions, we should further explore its potential for the development and implementation of preventive programs for elderly in the primary care setting. Before such programs can be realized in the population at large, several issues should be addressed.

First, future study should assess the effectiveness of internet-based interventions in primary clinical care settings. Although moderate effects of physical activity interventions have been shown in community dwelling elderly (4), they may not be directly generalisable to a primary care setting such as the general practitioners. As recruitment from the general population is likely to yield the best motivated participants, this might potentially result in an overestimation of the positive effects of the intervention. From a clinical perspective, it should be demonstrated that internet interventions yield positive results also in those who are potentially less motivated for behavioral change. Thus far, no study into the effectiveness of internet-based interventions in elderly has been performed in a primary care setting.

Furthermore, it is unclear what the adherence is to internet-based physical activity interventions after longer follow-up, and whether long-term health benefits can be expected. The very few long-term follow-up studies using daily life physical activity interventions showed a sustained increase in both physical activity and fitness using non-digital, face-to-face interventions (1; 7). This is promising as internet-based interventions may even be more successful due to their home-based nature, making them more accessible especially for older populations. This way, future internet-based intervention studies are able to, and should therefore, assess longer-term compliance and health outcomes, such as incidence of metabolic disease.

Finally, cost-effectiveness study should show that internet-based interventions provide the best value for money. While a large variety of physical activity interventions have been performed and shown to be effective in improving health, it is important to determine whether this success is cost-effective in terms of costs per gain of quality-adjusted life years (QALY). Promising data from cost-effectiveness studies of non-digital physical activity interventions suggest that costs are within the range of pharmaceutical interventions, and that cost-effectiveness is increased when direct supervision is not required (3). Whether this is also true for internet-based interventions and for older populations, should be shown in future studies. If this proves to be the case, internet-based lifestyle interventions may provide a welcoming alternative for pharmaceutical interventions in the promotion of health in older age and should then be considered for funding at a similar level.

CHAPTER 8. PERSPECTIVES

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