Physical exercise and dementia

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CHAPTER

7

General discussion

INTRODUCTION

The main objectives of this thesis were to study the role of physical activity in reducing the rate of cognitive and motor decline in institutionalized patients with dementia and to study how these effects reflected changes in activities of daily living (ADL). To do so, dementia related measurement tools to study intervention effects were inventoried and a new dynamic walking test was developed. Then, a specific combined aerobic and strength exercise program was developed and feasibility was evaluated. Finally, the cognitive, motor, and ADL effects of that program were assessed in patients with dementia.

MAIN FINDINGS AND THEORETICAL CONSIDERATIONS

Chapters 4 and 5 present data that support the hypothesis that it is feasible to conduct a combined aerobic and strength training program in institutionalized patients with dementia. Furthermore, such a combined aerobic and strength exercise program is superior in slowing down cognitive and motor decline when compared with aerobic-only training (chapter 5). This is illustrated in Figure 7.1. In contrast to the hypothesis however, we were not able to provide evidence that improvement in cognitive function is mediated by improved motor function. This finding suggests that other underlying mechanisms could be involved in delaying the cognitive decline in patients with dementia. Based on previous research, several underlying neurobiological mechanisms may be involved that support the choice for combining aerobic and strength training in one program to improve or stabilize cognitive and motor performance. Aerobic and strength training each can favorably influence levels of insulin-like growth factor-1 and brain-derived neurotrophic factors, which mediate growth, proliferation, survival, and differentiation of brain cells.[1] Strength training specifically may lower levels of the neurotoxic homocysteine, which is related to improved cognition.[2] Aerobic training specifically would have the potential to increase angiogenesis via vascular endothelial growth factor, thereby increasing cerebral blood flow, a key factor related to cognitive function.[3, 4] A limitation of the presented studies in this thesis is that no data was collected that may increase our understanding about the underlying mechanisms between exercise, motor changes, neurobiological change, and functional cognitive status in patients with dementia. To study these underlying mechanisms, blood-analysis (e.g., IGF-1, BDNF, homocysteine) and magnetic resonance imaging (MRI), if possible, could be considered.

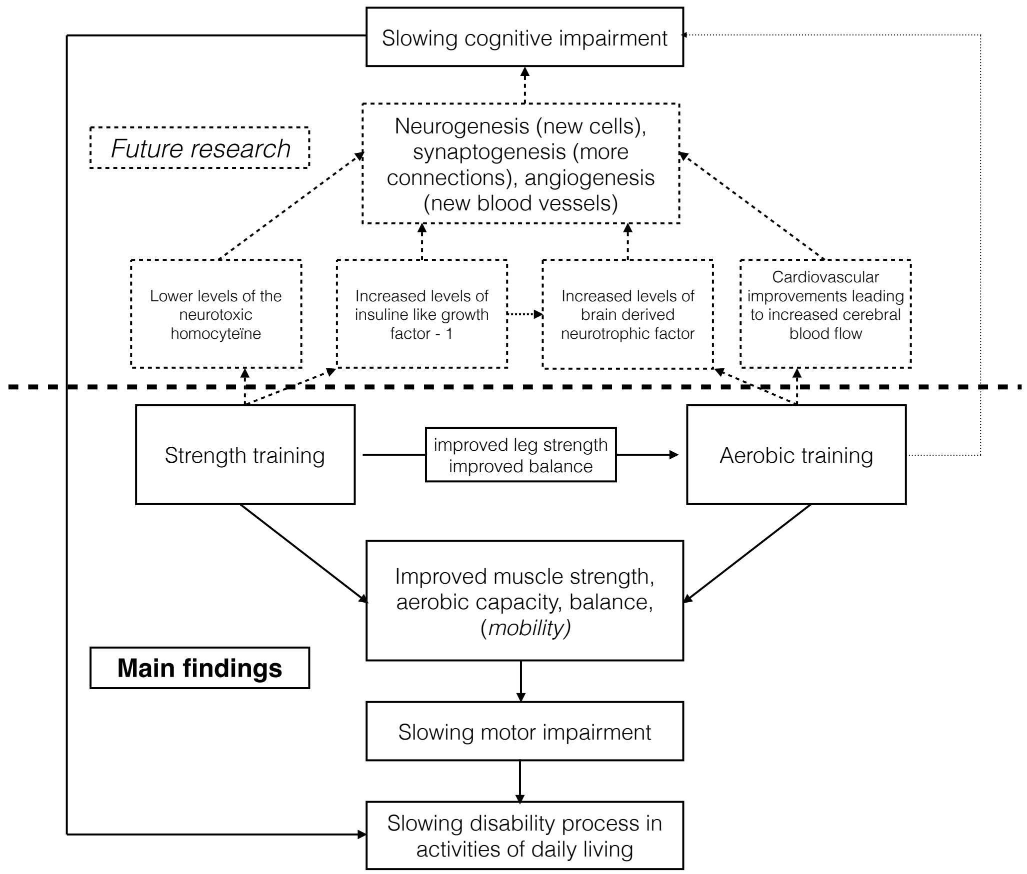

Figure 7.1. *Adjusted motor mechanism model that was presented in Figure 1.2, illustrating the main findings of this thesis and future research direction to study the underlying mechanisms between exercise, motor change, neurobiological change, and functional cognitive status in patients with dementia.*

Independent of the absence of mediation between improved motor function on improved cognition, both improved cognitive and motor function do mediate improvements in ADL (chapter 6), as illustrated in Figure 7.1. In pursuit of an Active & Healthy Ageing lifestyle for patients with dementia (Healthy Ageing Network Northern Netherlands, www.HANNN.eu), we therefore strongly recommend that future exercise activities should include both components of regularly aerobic and strength training to positively impact ADL in patients with dementia.

METHODOLOGICAL CONSIDERATIONS

Chapter 2 showed a large diversity in tests used in clinical trials in patients with dementia. It was striking that 59 different neuropsychological tests were used in 89 randomized trials. In other words, the majority of the clinical trials had used a set of different outcome measures. Another notable finding was that only 13 out of 89 randomized studies had used motor function tests, of which each study again used different tests. As a consequence of the large heterogeneity in cognitive and motor test use, systematic outcomes of meta-analytic studies are seriously hampered. With more homogenous test use, future meta-analytic studies could provide important insights in the development of effective intervention-based therapies. The neuropsychological tests that were used in the present thesis may be considered as feasible and sensitive tests to detect change in patients with dementia. Some tests however, were more difficult to successfully administer than others. Tests that were difficult to administer in patients with dementia who had a Mini Mental State Examination score lower than 15 out of 30 were the STROOP test[5], the Trail Making Test[6], the test for maximum quadriceps force[7], and the Figure of Eight test.[8]

For many of the tests used, only clinimetric properties were available for cognitively non-impaired older people or specific patient groups (e.g., CVA patients, Parkinson disease), while not being available for patients with dementia. Borrowing tests from other patient populations may harm the reliability and validity of the measurements in studies with dementia patients. On the other hand, researchers are limited in the number of tests in which the clinimetric properties for patients with dementia are shown to be adequate. During the development of the clinical trials in this thesis we obviously were confronted with this problem. As a first step to counter the lack of feasible and reliable measurement tools, chapter 3 described a new dynamic walking test, specifically developed for older patients with dementia. Critical features for test choice and test development in this population include: (1) that there are a small number of instructive steps per task, (2) that each task is of a short duration, (3) that there are no repetitive instructions needed during task performance.

To conclude, it is crucial that more feasibility and clinimetric research is done on neuropsychological and motor tests used in patients with dementia. Furthermore, normative data should be collected for different age groups, dementia types, and global cognitive status to enable researchers and clinicians to place changes in test performance over time in context of the specific sub-population of each individual patient. Researchers should come to a consensus on what feasible, reliable, and valid tests to use in future clinical trials in persons with dementia. Tests that were used in this thesis may serve as a basis for future development of such a core set of dementia-specific outcome measures and serve as a first step for a normative database in persons with dementia.

FEASIBILITY OF PHYSICAL EXERCISE PROGRAMS IN PATIENTS WITH DEMENTIA

In chapter 4 we showed that it is feasible for older patients with dementia to actively participate in a high frequency, combined aerobic and strength training program. In 2015 all elderly care facilities implement the so-called ‘bouwstenen’ (i.e., Dutch for ‘blocks’)[9], which are aimed at increasing physical activity as part of responsible elderly care in The Netherlands (see: www.nisb.nl). These ‘blocks’ are designed to help healthcare institutions implement physical activity in the care environment to prevent sedentariness (e.g., do more ADL tasks, walk to activities instead of using wheelchairs). The building blocks include items that help with client binding, creating a physical activity infrastructure, and integrating physical activity in the care environment. In addition to promoting such basic everyday physical activities to prevent sedentariness, structural physical exercise programs, as presented in the current thesis, can also be a strategy to decrease sedentariness. Such an exercise program can maintain or improve cognitive and motor function, which are important aspects for ADL[10-12] and quality of life.[13]

To date, most physical exercise programs that are offered in the care environment are group based. Group-based training, however, may lead to difficulties in controlling for exercise quality per individual. When planning to implement physical exercise programs for patients with dementia it is important to note that dementia is often related to behavioral problems, such as apathy and agitation, which may cause inactivating thoughts and difficulties in initiating physical activity and participating in exercise activities.[14] Furthermore, the large heterogeneity in patients with dementia in a long-term care setting practically means that there is a difference in the ability of each patient to successfully participate in exercise programs. In addition, it is known that frail participants may benefit from individualized interventions, while group interventions are successful for the less disabled.[15, 16] Thus, it seems that individually guided sessions are a prerequisite to monitor and motivate participants to stay sufficiently involved in an exercise program.[16] Therefore, when implementing exercise programs in a long-term care setting with frail older people, an individual approach may be better than a group-based exercise approach.

Another argument why an individualized program may enhance participation, is that the one-on-one supervised exercise format (as presented in chapters 4 and 5), contributed to high adherence (~90%), low drop-out, as well as exercise performance according to protocol, and no program related adverse events other than muscle soreness. In other studies, similar high adherence rates were found after specific one-on-one exercise programs in patients with dementia.[17-19] Together, the one-on-one exercise adherence rates were approximately 30%-60% higher than several group exercise programs in frail older people and patients with cognitive impairment.[16, 20, 21] However, a recently published paper on a group-based (i.e., 4 participants per group) aerobics-program in patients with dementia showed adherence that was similar (i.e., ~90%) to our and other one-on-one studies. This group-intervention study consisted of aerobics in an exercise group of no more than four patients per group with one trainer.[22] Although the use of group interventions can be more easily defended from a policy point of view, based on the findings of this thesis, there is reason to believe that a more individual approach is the most successful way in keeping adherence and exercise quality high in patients with dementia.

MONITORING EXERCISE PROGRESSION IN PATIENTS WITH DEMENTIA

With personalized exercise diaries it is possible to monitor the content of the exercise program and the progression of each participant closely. Such a diary can enable researchers and clinicians to monitor and adjust the intensity of the exercise program on an individual basis, so that during every training session a moderate to high intensity exercise training is offered. Moreover, overload or injury that may lead to drop-out can be detected at an early stage and prevented. The study described in chapter 5 was the first to include detailed information on the training sessions, including heart rate during exercise, Borg score for exercise intensity, and exercise duration. Based on our exercise-diary experience, some improvements can be proposed to monitor exercise even more precise and more reliable. For outside use, we suggest to use Global Positioning Systems (GPS) to more closely monitor the total distance covered and the walking speed. Also, the use of sensor technologies and accelerometry, which are built-in in iPod, may enable a more close registration of gait characteristics, including step symmetry and step frequency. These systems are currently under development[23-25], and could give extra information about the progression or deterioration of gait characteristics, which are proposed to be closely related to the quality of movement, fall risk, and also executive functioning.[26-28] Such intermediate measurements could also be done in a control group as a reference for training effects in the exercise group, and to get insight into possible fluctuation of motor performance over time in patients with dementia. Furthermore, the use of heart rate and blood pressure monitoring systems during exercise can give better insight in the intensity level during exercise. This is important because in the studied intervention in chapter 5 the heart rate was measured when the participant was already in a chair after exercise and resting. Also, more precise time registration of active and passive time during an exercise session can enable researchers to better calculate the total exercise load (e.g., exercise volume (minutes) * training intensity, such as average heart rate or rate of perceived exertion). For future research into the

dose-response relationship, when studying the tradeoff between exercise load and cognitive-motor improvements, it is of utmost importance to monitor the exercise quality and quantity as closely and accurately as possible. Of note, however, is that the amount, and thereby the burden of measurements taken, should not limit the participant in their exercise adherence or constrain functioning in daily life.

EXERCISE TO AFFECT PHYSICAL AND COGNITIVE FUNCTION

In the introduction it was proposed that exercise as an extra-individual factor may prevent decline or even improve motor and cognitive function, which are considered key elements in preventing or slowing down the ADL disability.[10] Chapter 5 showed that a combination of aerobic and strength training affected cognitive and motor function in patients with dementia, and was superior compared to aerobic-only training.

A striking result of the studies in chapter 5 and 6 was that the non-exercise Social group showed a decline in both cognitive and motor function over a relatively short period of time (i.e., 9 weeks and 18 weeks). Although the aim of this thesis was to study the effects of physical activity in patients with dementia, the presented decline in both cognitive and motor function in the non-exercise group is alarming because recent work reported that nine out of ten patients with dementia in Dutch nursing homes are physically inactive.[29] The consequences of physical inactivity and sedentariness have not yet been studied carefully. An inactive lifestyle due to the institutionalized care environment, but also due to living longer at home, is a common situation and requires urgent attention from future research. However, to better study the effect of physical inactivity versus physical activity, data is needed that quantifies the total volume of sedentariness and physical activity. Such data could be collected with accelerometers[30] , and could serve as a basis to control for basic activity level. Furthermore, the nature and total volume of physical (in)activity, and the significance of the extra exercise program could be studied.

For patients with dementia it is crucial to stay physically active over a longer period of time because most of the direct effects disappeared after participants quitted the exercise programs, as shown in chapter 5. This observation is of critical clinical importance and calls out for a structural approach of physical exercise on a daily basis or a more physically active lifestyle. An important follow-up question is whether the improvements in the combined exercise group will continue or that a ceiling effect will stop the observed improvements. Based on the current short-term findings, the differences between physically active and passive patients may be larger after a longer period of time. Active patients showed a higher motor and cognitive performance level and were less affected during the delayed 18-week measurements than their peers in the social non-exercise group (chapter 5).

In sum, a lesson for professionals and researchers is that physical activity programs should both include aerobic and strength components to prevent further decline, or even improve, cognitive function. Conventional walking-only programs may not be enough to conserve or slow down the deterioration of cognitive and motor function but a combination of strength training with aerobic training seems the key to reach these beneficial effects. A change in physical activity pattern can result in beneficial cognitive and motor changes over a relatively short period of time. Longer periods of exercise are needed to maintain these changes over time and prevent a fallback of cognitive and motor function.

CRITICAL REFLECTIONS

The generalizability of the presented work is limited to a specific segment of patients with dementia. The institutionalized patients who participated were mobile and willing to participate. For the remaining group of patients, including those who were unable to walk on their own, experienced a lack of motivation, or were unable to understand instructions, we must identify other training strategies. For example, wheelchair based training protocols adopted from rehabilitation practices.[31]

In the presented studies of this thesis, sub-analysis between different types of dementia was difficult due to the small sub-groups of dementia types. Moreover, determining the onset and type of dementia is problematic because, in general, the medical files do not specify exactly which type of dementia a patient has been diagnosed with. If the type of dementia was specified, this still remains an indication because a definite diagnosis can only be confirmed at post-mortem or through a brain biopsy.

As described in chapter 5, the interpretation of the results should be done with caution because cognitive and motor measurements in patients with low cognitive ability (i.e. MMSE 9 – 14) may be less reliable compared with measurements in cognitively less impaired patients (i.e. MMSE > 15). This was shown by a reliability study of six motor tests in patients with dementia.[32] A possibility to decrease the measurement error and improve the reliability is to perform multiple pretest and posttest measurements and average the scores of those measurements or take the maximum score.

In the presented studies of this thesis, no sub-group analyses were performed between responders and non-responders. Such analyses could provide valuable

information on the patient characteristics in light of exercise benefits. In line with these recommendations lies the question whether training duration and intensity play a role in cognitive and motor effects, which is an understudied subject so far. Future studies should be designed to examine the dose-response relationship, which is of clinical relevance because low intensive exercise programs are easier to integrate in daily life compared to high intensity exercise programs.

PRACTICAL IMPLICATIONS

Independency in activities in daily life is related to a higher quality of life in patients with dementia.[13] In light of 'Exercise is Medicine'[33], chapter 6 is the first study to show that improvements in ADL are mediated by specific improvements in walking endurance, muscle strength, and global cognitive function. This again underlines the importance to support systematic physical exercise programs in the care setting to affect these functional aspects, thereby positively influencing the disablement process (see Figure 1.1). The relation between motor and cognitive changes as shown by the mediation analysis in chapter 6 point in the direction that physical exercise can translate into improved ADL, and therewith lead to improved quality of life.[13]
In light of the Healthy Ageing spear point of the University Medical Center Groningen (see: www.healthyageing.umcg.nl), the collective studies in this thesis have provided additional insight in the cognitive, motor, and ADL effects after specific forms of physical exercise in older patients with dementia. The knowledge provided in this thesis can help to substantiate the argument that physical exercise in an institutionalized care setting, or at home, needs more attention. Below, some action points for health professionals, policy makers, and relatives are given:

Know each individual (both patients and relatives)
Before people with dementia enter a nursing home, get a grip on their current physical activity level and willingness to participate in exercise programs. Then, provide physical activity and exercise options to enable family and volunteers to get involved (e.g., walking routes, strength exercise guidelines, material, etc.).

Monitor physical activity
Monitor the daily routines and activity patterns of patients with dementia in a personal activity diary. This can help to implement physical activity and exercise at the right time of the day, thereby possibly preventing refusal, exercise overload, and injury, which are important factors in becoming physically active or inactive.

Seduce patients to become physically active
Nursing homes should take into account the possibilities in becoming physically active inside and outside the care facility. Invest in a safe environment to seduce and to accommodate residents in becoming physically active or stay active as long

as possible (e.g., take the stairs, walk for coffee).

Revise existing physical exercise programs

Evaluate existing physical exercise programs and focus on moderate intensity aerobics and strength training of large muscle groups (e.g., legs). Elicited motor and cognitive effects may provide a basis to participate in other activities.

Educate the work place

Provide education about physical activity to all primary care staff to advise and coach patients, spouses, family, and caregivers on basic physical training options and opportunities inside and outside the nursing home.

Educate upcoming professionals

The importance of physical exercise should be emphasized during (under)graduate training of all health professionals.

Work as a team

Organize and stimulate visitors in care institutions to also bring along other patients during (physical) activities.

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