Determinants of muscular and functional vitality in oldest old people

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Summary

10.1 Introduction

The aim of the research presented in this thesis was to study candidate determinants of muscular and functional vitality during ageing. The first part of this thesis focused on the functional phenotype with an emphasis on handgrip strength, gait speed and functional abilities. In the second part of the thesis the focus was on possible determinants of muscle weakness in oldest old people. The underlying motivation for this research was to gain insight into possible causes and consequences of ageing muscle and functional decline with the objective to enable elderly people to age more successfully in future by prevention or treatment of possible causes.

10.2 Muscle weakness, functional disability and mortality

Declining muscle mass and muscle strength, referred to as sarcopenia and dynapenia, are prevalent features in very old people. Some report prevalences of sarcopenia as high as 60% in the general oldest old population [1]. Since demography changes dramatically, by 2050, oldest old people will account for one-fifth of all older persons globally; one can presume that sarcopenia and dynapenia will become common health problems in due course [2]. Hence, muscle strength has an important impact on general health of elderly people. Muscle weakness is associated with declining physical fitness, increased disability, cognitive decline and mortality [3-18]. Functional measurements, such as gait speed, predict functional limitations of the lower body, cognitive decline and survival in older people. [13, 19-22]

All these associations raise the question about the value of muscle strength and functional tests as gait speed as markers or predictors of adverse health outcomes in oldest old people. Such a test could be a useful part of the clinical evaluation of very old patients in determining which patients are most at risk of accelerated decline in the near future and who could still benefit from interventions. Furthermore, knowledge about survival might benefit patient's wellbeing and quality of life because it could improve clinical decision making with regard to treatment prognosis.

10.3 Study populations

10.3.1 Leiden 85-plus Study

The main body of the research presented in this thesis is part of the Leiden 85-plus Study. The Leiden 85-plus Study is a community-based prospective follow-up study of inhabitants of the city of Leiden, the Netherlands. Enrolment took place between 1997 and 1999. All inhabitants, including nursing home residents, who reached the age of 85 years, were eligible to participate. There were no selection criteria on health or demographic characteristics [23]. In total 599 persons participated, 87% of all eligible inhabitants. At baseline, a research nurse visited participants at their place of residence. During these visits, face-to-face interviews, and performance tests were conducted. Also a blood sample was taken and the electrocardiogram was recorded. Follow up visits were performed annually for a period of five years and follow up on survival still continues. All subjects were followed up for survival until January 2010 with a follow-up period of 12.2 years. Dates of deaths were obtained from the Dutch civic registry.

10.3.2 Leiden Longevity Study

For purposes of comparison with the oldest old population, the middle aged participants of the Leiden Longevity Study are included in two studies presented in this thesis. In the Leiden Longevity Study, 420 families were recruited consisting of long-lived Caucasian siblings together with their middle aged offspring and the partners thereof [24]. There were no other inclusion criteria for the offspring, other than being offspring of the nonagenarian siblings or being the partner of the offspring. Our studies included the cross-sectional baseline sample of the middle aged offspring and their partners (n= 670). All participants visited the study center where all measurements were taken.

10.4 Functional phenotype as predictor of health and survival

10.4.1 Handgrip strength as a predictor of health and survival

The aim of the studies described in chapters 2 and 3 was to study the predictive properties of handgrip strength with regard to functional, psychological and social health domains and survival. Handgrip strength was used as a proxy for muscle strength. The findings showed that low handgrip strength was a predictor of accelerated dependency in activities of daily living and also predicted accelerated cognitive decline. Based on these results it was concluded that measuring handgrip strength could be a useful instrument in geriatric clinical practice to identify those oldest old patients at risk for accelerated decline in these domains. The importance of handgrip strength measurement as a screening tool was further emphasized by the finding that lower handgrip strength and a steeper decline in handgrip strength over time were both associated with a twofold increased mortality risk and could therefore serve as a means for prognostication in very old patients. However more studies are needed into this matter in other populations, such as patients admitted to clinical wards and outpatient clinics.

10.4.2 Gait speed, functional ability and survival

The study of the association between gait speed and survival in a population of oldest old participants is described in chapter 4. This study showed that gait speed was associated with survival in oldest old people aged 85 years with a follow up of 12 years. However, the predictive value of gait speed in very old people was weakened by cognitive decline, depressive symptoms, disability in instrumental activities of daily living (IADL), and sedentary life style, all common features in geriatric practice. Inability to perform a walking test was highly discriminative of poor survival. Furthermore, IADL disability was associated with a higher predictive value for poor survival in oldest old people compared to gait speed, independent of common confounders and gait speed. With regard to prognostication in very old individuals the value of gait speed should be reconsidered. In those unable to walk, simple IADL assessment by questionnaire which is already part of the comprehensive geriatric assessment is possibly a better predictor than handgrip strength and gait speed with regard to survival.

10.4.3 Functional disability and depressive symptoms over time

In chapter 5 the results of the study of the longitudinal associations of depression and depressive symptoms with cognition, chronic diseases and functional ability in oldest old people are presented. The findings of this study suggest that current functional ability at age 85 years in personal (ADL) and instrumental activities (IADL) of daily living is primarily associated with depressive symptoms in oldest old people. Over time IADL disability was associated with an increase in depressive symptoms at age 90 years. Moreover, increasing ADL and IADL disability during follow up was associated with an increase in depressive symptoms at age 90 years. This association was independent of cognitive functioning for people with mild dementia or normal cognitive functioning, and comorbidity. Surprisingly, depressive symptoms at 85 years were not associated with increased functional disability in oldest old people. These are strong reasons to detect and intervene with older people with declining functional ability as a possible means to prevent depressive symptoms during ageing. Further clinical studies should determine whether rehabilitation therapy could contribute to improvement in depressive symptoms.

10.4.4 The temporal relationship between cognitive performance and muscle weakness

Cognitive decline and muscle weakness are prevalent health conditions in elderly and often co-occur in elderly persons. The temporal relationship between decline of muscle strength and cognitive performance is still unclear. Does poor handgrip strength precede and therefore mark cognitive decline or is the opposite the case. In the study into this relationship described in chapter 6 better cognitive performance was associated with better muscle strength and a slower decline in muscle strength. In the longitudinal analysis better baseline cognitive performance, in particular attention, processing speed and memory function was associated with slower decline in handgrip strength, whereas low baseline handgrip strength was not associated with an accelerated decline in cognitive performance. This suggests that cognitive decline precedes muscle weakness. Cognitive decline in elderly subjects should make clinicians vigilant for muscle weakness in the near future. Further clinical research is needed to assess suitable interventions.

10.5 Candidate determinants of muscle weakness in oldest old people

10.5.1 The association between blood pressure and muscle strength

In chapter 7 the longitudinal association between blood pressure and handgrip strength is presented. This association was studied in oldest old people (Leiden 85-plus Study) and middle aged people (Leiden Longevity Study). Results showed a positive association between systolic, diastolic and pulse pressure and handgrip strength in oldest old people. In addition, declining systolic, diastolic and pulse pressure were associated with a decline in handgrip strength during follow up. Blood pressure was not associated with handgrip strength in the middle aged people. A possible hypothesis explaining this counterintuitive finding of a higher blood pressure being beneficial is described. In short, ageing is associated with increased peripheral vascular resistance and a reduction in vasodilation capacity. Increased vascular resistance during the ageing process requires higher pressure as a mechanism to maintain tissue perfusion as a means to prevent further ischemic end organ damage in kidney, brain and skeletal muscle. It is clear from these findings that further research is needed into the implications of hypertension and antihypertensive treatment in the general population of oldest old and whether the improvement on cardiovascular endpoints comes at a cost of muscle weakness in this population.

10.5.2 Insulin like Growth Factor-1 and muscle strength in middle aged and oldest old

The assessment of the association between Insulin-like Growth Factor-1 (IGF-1), IGF binding protein 3 (IGFBP-3) and functional outcome in middle-aged and oldest old people is described in chapter 8. The results show that levels of IGF-1 and its binding protein, IGFBP-3 both decrease with age and that they are positively associated with muscle strength in postmenopausal middle-aged and oldest old women, but not in men. Furthermore, we found that serum levels of IGF-1 were negatively associated with walking speed in oldest old men and IGFBP-3 serum levels were positively associated with activities of daily living in oldest old women. However, further research is needed to explain the found gender differences in IGF-1 signaling in muscle in oldest old subjects. The age-related decline in GH and IGF-1 serum levels may promote frailty by contributing to the loss of muscle mass and strength. Maintenance of higher

IGF-1 levels could therefore contribute to preservation of muscle function and subsequent muscle performance in an elderly female population.

10.5.3 Innate cytokine production capacity and muscle weakness

To study whether a systemic inflammation or merely a high innate production capacity of TNF-α contributes to decline of muscle strength in elderly people, we studied the relation between the ex-vivo production capacity of pro- and anti-inflammatory cytokines and changes in handgrip strength within a prospective population-based follow-up study of elderly people aged 85 years and over in chapter 9. We showed that it is not the actual inflammatory state, but a high production capacity of pro-inflammatory cytokine TNF- α that precedes a greater decline of handgrip strength in old age. The association with production capacity of TNF- α was not changed by adjustments for production capacity of the other cytokines, thus supporting the hypothesis that TNF- α signaling contributes to muscle weakness in elderly people. The association between innate cytokine production capacity and development of poor handgrip strength over time could be interpreted as an argument in favor of a causal relation. This relation is biologically not unexpected. TNF-α, first denoted as 'cachectin' has various pleiotropic actions among which there are inflammation and apoptosis.

10.6 Conclusion and future perspectives

In a population based cohort of oldest old people the functional phenotype was a strong predictor of survival and future functional ability. The results of the studies presented in this thesis allow us to speculate about the predictive value of functional measurements as markers of vitality in a clinical population of oldest old patients. Use of these markers of vitality could contribute to increased vigilance in clinicians for increased risk of health problems in their very old patients, such as depressive symptoms, cognitive decline, disability in activities of daily living and mortality. Furthermore, these vitality markers could be helpful in individual prognostication and decision making in very old patients who are faced with serious illnesses. However, the value of handgrip strength, gait speed and ability in instrumental activities of daily living now needs to be studied in appropriate clinical populations of oldest old patients.

With regard to candidate determinants of muscle weakness in oldest old people the finding that higher blood pressure is associated with better muscle strength over time is interesting. First, it contributes to the finding of others [25,26] that higher blood pressure in elderly seems overall beneficial and not necessarily harmful in oldest old persons with regard to muscle strength. Second, it encourages us to reevaluate current guidelines on hypertension treatment in aging populations, thus promoting further clinical research into the association between blood pressure and healthy aging in very old people.

TNF-α innate production capacity is another strong determinant of future muscle weakness independent of comorbidity or production capacity of other cytokines. This is of interest because the innate production capacity is largely a hereditary trait [27]. Further research needs to be done to confirm these results in other populations of elderly people. If so, anti TNF-α therapy could possibly be a means to prevent or treat sarcopenia in elderly at risk.

In women aged 90 years, muscle strength is associated with higher levels of IGF-1, but not in men. It is of interest to study the longitudinal association between IGF-1, the binding protein IGFBP3 and muscle strength in ageing men and women. This results hints at a gender difference in IGF-1 signaling with regard to muscle tissue. And yet again, further research needs to be done to establish whether maintaining hormone levels could contribute to muscle vitality.

10.7 References

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