Chapter 14
General discussion
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To elaborate on and raise awareness about the relevance of poor muscle status among clinicians, researchers and the general public, we aimed to investigate diagnostics, determinants and consequences of poor muscle status. With respect to diagnostics, we identified a lack of knowledge among the general public, while the definition of sarcopenia is still changed by clinicians and researchers with substantial clinical impact. Consequences of poor muscle status in older hospitalized patients were found to include geriatric syndromes, falls, dependent living and mortality. To prevent further consequences, healthcare professionals should notice acute versus elective admission, patients with poor cognitive functioning, increased inflammation, and a higher body mass index predicting the pre-disease metabolic syndrome as determinants of poor muscle status. To support clinical diagnostics, instrumented assessments are fast approaching, among which the daily-life gait speed monitoring and instrumented physical performance tests via mobile technology that were investigated in this thesis. These instrumented assessments yield different information about muscle status compared to standard clinical tests using a stopwatch to measure performance. However, an additional benefit of these instrumented tests in discriminating between self-reported functional status, on top of the standard clinical tests, was not observed. By appreciating the impact and importance of healthy muscle status in clinical practice, clinicians and researchers may collectively contribute to prevent further deconditioning of our older patients.

A major asset of this thesis is the availability of multiple cohorts. An overview of the mean muscle status of the different cohorts that were investigated throughout this thesis is presented in Figure 1. This figure shows a generally lower handgrip strength and gait speed in both older outpatient and inpatient cohorts compared to community-dwelling adults. In the inpatient cohorts (EMPPOWER and RESORT), mean handgrip strength and gait speed were below the sex-specific cut-off values for sarcopenia\textsuperscript{126}, indicating poor muscle status in hospitalized patients (see Figure 1). The observed poor muscle status among outpatients and inpatients highlights the importance of public and professional knowledge on this matter and the need for developing effective interventions to counteract poor muscle status. Figure 1 will be used as a directory throughout general discussion, with reference to the cohorts included in various chapters throughout this thesis.

Public knowledge and clinical use of definitions and diagnostics

In part 1, diagnostics, we showed that the general public is not aware of the existence and treatment of sarcopenia (see Figure 1; Sarcopenia awareness cohort, chapter 2), and that clinicians and researchers are still changing the definition for sarcopenia, which has consequences for diagnostics (chapter 3). If clinicians and researchers are not able to agree upon a definition for sarcopenia\textsuperscript{73}, and if clinicians do not know how to formally diagnose sarcopenia\textsuperscript{60}, how is the general public supposed to understand what sarcopenia entails? Applying the new European definition for sarcopenia from 2019\textsuperscript{126} instead of the definition from 2010\textsuperscript{10} resulted in differences up to 55% in prevalence of sarcopenia in eight cohorts of older adults. Age-related decline in muscle status is expected to start around the third decade of life\textsuperscript{85}, yet the
Figure 1. Mean muscle status in the thirteen cohorts included in this thesis, ordered by age and health status. Green dotted lines indicate normative values for adults aged 65 years. Red dotted lines indicate cut-off points for sarcopenia.
Sarcopenia Awareness cohort (see Figure 1; chapter 2) expected muscle mass to decline on average from 46 years onwards. Fortunately, the Sarcopenia Awareness cohort (see Figure 1; chapter 2) was aware of the importance of healthy muscle status: the importance of muscle for overall health had a median score of 91 out of 100 (IQR 83 – 95), and the score was even higher regarding the role of muscles in staying independent at older age (median 92, IQR 88- 96). It has to be noted that the included population was highly educated, had on average a good muscle status (see Figure 1; Sarcopenia Awareness cohort), and was interested in healthy aging. Therefore, the results may not be applicable to overall society and are in need of further investigation.

The history of the introduction of the term “sarcopenia” is sometimes compared to osteoporosis, because of shared causes and interventions. Sarcopenia was first described in 1989\(^{486}\), the first working definition was proposed in 1998\(^{139}\) and classified as a disease in 2016\(^{59}\). Osteoporosis was first described in 1835, the first consensus definition was proposed in 1992, and classification as a disease shortly thereafter\(^{487}\). In a study in 2001 among highly educated females, only 13.7% of participants had not heard about the disease\(^{105}\). In two to three decades, the term “sarcopenia” may be as well-known to the public as osteoporosis, although acceleration of this process would benefit societal health. The knowledge about the importance of healthy muscle status among the general public provides opportunities for prevention and treatment, but more attention needs to be paid to muscle status in clinical practice\(^{60}\). We need consensus on the definition of sarcopenia\(^{73}\) and subsequently select the most effective interventions to counteract poor muscle status, to be able to educate the general public on the consequences and motivate them to adequately prevent the development of poor muscle status.

**Short- and long-term consequences of poor muscle status in the hospital**

Educating the general public may help to prevent the consequences of poor muscle status in older hospitalized patients, as investigated in part 3, consequences. Recent studies showed that during hospitalization, patients with poor muscle status experience short-term adverse events such as a longer length of stay, in-hospital surgical and infectious complications, and in-hospital mortality\(^{304,78}\). In EMPOWER the average muscle status in older inpatients was poor at admission to the hospital (see Figure 1; EMPOWER cohort), and this was associated with a higher risk of malnutrition, delirium, falls and disability, collectively termed geriatric syndromes (chapter 11). Longer-term consequences of poor muscle status after hospitalization include readmissions\(^{304}\), institutionalization\(^{78}\), and in EMPOWER we observed a higher risk of post-hospitalization falls, dependent living and mortality three months after discharge (chapters 12 and 13). EMPOWER was an inception cohort including all older inpatients seen in daily clinical practice with a defined time-window, which induced heterogeneity in admission diagnoses, morbidities and interventions applied during the hospital stay. In chapters 11 and 12, an unexpected difference between males and females was observed; the associations between muscle status, geriatric syndromes at admission and falls after hospitalization were only significant in males. Sex differences in muscle measures, determinants and consequences have previously been reported but are not well explained\(^{488,489}\). Females might
exert a greater vulnerability to negative effects of multimorbidity compared to muscle status\textsuperscript{490}, but this is speculative and needs clarification in future research. In prior research after one year follow-up, a substantial proportion of patients still suffers from functional impairment and morbidity\textsuperscript{17} and every subsequent readmission may create more dependency eventually resulting in permanent disability\textsuperscript{95}. Depending upon others for care significantly reduces quality of life\textsuperscript{491}. We showed that poor muscle status is associated with geriatric syndromes, falls, dependent living and mortality, hence muscle status is a strong potential target to improve clinical outcomes.

**Acute or elective hospitalization and other determinants of poor muscle status**

To prevent adverse consequences of poor muscle status, part 2, determinants, investigated the identification of at-risk patients during hospitalization. To identify older patients at risk of poor muscle status who are targets for (personalized) preventative interventions, individual characteristics need to be identified that can predict poor muscle status, predisease states and further impairment. For this purpose we investigated metabolic syndrome, acute versus elective hospitalization, cognitive functioning and inflammation in various older populations. Metabolic syndrome is a highly prevalent predisease state\textsuperscript{394} and is associated with poor muscle status\textsuperscript{79,492}. We showed that the incidence of metabolic syndrome can be predicted using body mass index in older community-dwelling adults (see Figure 1; LASA cohort, chapter 10). By application of similar interventions, prevention of obesity contributes to prevention of poor muscle status and this provides an interesting dual target for clinical practice\textsuperscript{79,492}.

Our systematic review of the literature (chapter 6) showed that elective hospitalization of older patients resulted in a decrease in muscle mass and muscle strength, but this was not the case in older acutely hospitalized patients. This finding was confirmed by results of the EMPOWER study (see Figure 1; chapter 11); acutely admitted older patients increased in handgrip strength from admission to discharge, and did not change in muscle mass. Hypothetically, electively admitted patients have larger physical reserves and are more prone to a decline in muscle status, therefore, the impact of hospitalization is more evident. This creates a need for pre-hospital interventions such as prehabilitation before elective surgery, chemotherapy and radiation\textsuperscript{66-68}. Acute hospitalization encompasses a period of acute illness before admission, the hospital stay and recovery after discharge. From experimental immobilization studies, muscle is expected to deteriorate at a fast rate in the first few days of acute illness, immobilization and catabolism, and then reaches a plateau\textsuperscript{493}. Two-third of the acutely hospitalized patients decline in activities of daily living (ADL) score in the acute illness period before hospitalization and one-third between admission and discharge\textsuperscript{7}. In the RESORT cohort (see Figure 1; RESORT cohort) 88% of the patients reported to decline in ADL score from two weeks before acute hospitalization to discharge. In EMPOWER we observed that acutely admitted older patients had poor muscle status at admission to the hospital, with the mean below cut-off points for sarcopenia (see Figure 1; EMPOWER cohort), and a further decline in muscle status was not expected nor observed (chapter 11). A recent systematic review by Hartley and colleagues\textsuperscript{494} found handgrip...
strength to increase slightly during acute hospitalization in adults aged ≥ 18 years, while knee-extension strength declined. Combining these findings with our results creates the hypothesis that most of the muscle deterioration occurs before acute hospitalization, with some further deterioration of lower extremity strength during hospitalization. This supports the premise that different approaches to prevent poor muscle status are needed in elective versus acute hospitalization.

In hospitalized older inpatients and geriatric outpatients, lower cognitive function (see Figure 1, EMPOWER cohort, chapter 7) and higher inflammatory markers (see Figure 1, COGA and RESORT cohorts, chapters 8 and 9) were associated with lower muscle mass, muscle strength and physical performance. In the COGA and RESORT cohorts (see Figure 1; COGA and RESORT cohorts, chapters 8 and 9) we used CRP, albumin and ESR as markers for inflammation because of their wide availability and use in clinical practice. Limitations apply because these markers are generally used as nonspecific indicators for infection, lacking evidence-based cut-off points for the older hospitalized population. Applying clinically used cut-off points for CRP (10 mg/L) and albumin (35 g/L) result in a high prevalence of inflammation in the older hospitalized cohorts: In the RESORT study we found that 79% of patients had a CRP > 10 mg/L and 93% had an albumin < 35 g/L, and in EMPOWER 82% of patients had a CRP > 10 mg/L and 76% had an albumin < 35 g/L during hospitalization. We showed that repetitive measurements and combining markers into clusters of CRP and albumin could provide additional information to predict poor muscle status. Our results suggest that CRP, albumin and ESR could serve as a primary assessment to identify at-risk patients. Subsequently, cytokines like IL-6 and TNF-α can be used for secondary classification, but this is in need of further investigation.

Another potential determinant is cognition: In EMPOWER (see Figure 1; EMPOWER cohort, chapter 7) poor cognitive function was associated with poor muscle status, highlighting the brain-muscle interaction in this older inpatient population. Determinants to predict muscle status in clinical practice may sometimes be termed biomarkers, described as “a characteristic that is objectively measured as an indicator of normal biological processes, pathogenic processes or pharmacologic response to a therapeutic intervention” \(^{495}\). Many biomarkers potentially influence muscle status during hospitalization \(^{33}\), and inflammation is a significant contributor due to proteolysis accompanying the catabolic state \(^{9}\). In geriatrics, the benefit of a comprehensive biological assessments is increasingly recognized \(^{496}\), and the usefulness in the hospital setting is worth exploring in future research.

**Utilizing instrumented measurements in diagnostics**

Muscle status shows a gradual age-related decline \(^{53-55}\), often lacking warning signs before impairments arise or are detected at admission to the hospital. Instrumented measurements like daily-life gait speed and physical performance tests provide additional information beyond current clinical physical performance tests that use a stopwatch. We observed a gap between 4-meter gait speed and instrumented daily-life gait speed (see Figure 1; GreyPower 1 cohort, chapter 4); Gait speed measured using the standardized test was higher and uncorrelated to daily-life gait speed. We also tested smartphones that can measure and provide us with detailed features of instru-
mented physical performance tests, like the instrumented timed up and go test and chair stand test (see Figure 1; PreventIT cohort, chapter 5). The measured features include information about sub phases of the tests, and could increase sensitivity of the tests and potentially assist in identifying adults at risk of deconditioning. For the instrumented Timed Up and Go, 29 features were available, and for the instrumented Chair Stand Test 21 features were available. These features are hard to interpret and are not yet suitable for use in clinical practice. An additional accuracy of the instrumented physical performance tests, on top of the standard clinical tests, was not observed when discriminating between adults with high versus low self-reported functioning (chapter 5). Our findings are similar to a previous study that observed similar effect sizes for instrumented versus standard clinical gait speed and chair stand tests associated with calendar age\textsuperscript{76}, although some additional characteristics of gait obtained with the instrumented tests were also associated with calendar age, including a longer stride time, lower movement intensity and harmonic ratio in ML and AP direction and a higher amplitude of the dominant frequency in VT direction\textsuperscript{76}. In another study, instrumentally measured sit-to-stand transitions were more strongly associated with self-reported health status, self-reported functional status and the Short Physical Performance Battery score, compared to manually recorded sit-to-stand transition time\textsuperscript{75}. In conclusion, the added value of instrumenting measurements may include a higher precision in identifying at risk patients, a different construct of muscle status and additional characteristics of physical performance, yet this needs further investigation before application in clinical diagnostics. It is important to learn which features are most informative regarding muscle status and health and how to simplify the interpretation of the collected signals.

**Challenges in counteracting poor muscle status in hospitalized older adults**

Evidence based interventions to counteract poor muscle status consist of (sub) maximal resistance training and protein supplementation\textsuperscript{98,107,108}, although these are challenging to implement in the acute care setting\textsuperscript{74}. A recently published systematic review on the effects of physical interventions in geriatric patients during hospitalization\textsuperscript{497} showed that applied interventions differed substantially in difficulty level, included small numbers of participants and assessed different outcomes\textsuperscript{497}. Some interesting technological applications were used to assist in providing the interventions\textsuperscript{497}. Demanding physical exercises are often not possible in the acute setting due to immobilization and fatigue\textsuperscript{498}. Besides physical interventions, nutritional supplementation of protein promotes muscle protein synthesis and reduces the effect of anabolic resistance from immobilization\textsuperscript{392}. However, disease related anorexia, poor dental care and poor absorption contribute to a high prevalence of malnutrition during hospitalization\textsuperscript{27} and complicate nutritional interventions. An additional obstacle for effective physical and nutritional interventions is the short duration of hospital stay; on average five days in EMPOWER (see Figure 1; chapters 7, 11-13) and seven days in RESORT (see Figure 1; chapter 9). Currently, evidence for effective interventions to counteract poor muscle status consists of a longer duration of at least three months\textsuperscript{499}, whereas evidence for the effectiveness of short-term interventions of only a couple of days is nonexistent. The few
days in the hospital are often filled with diagnostics and are demanding for the patients, so it remains debated whether it is feasible to apply any interventions during this time-window. Hospitalization could providing a screening opportunity of patients at risk of (development of) poor muscle status, and provide the start of prevention and treatment with a longer intervention period after discharge. Whether these interventions should consist of multimodal, personalized programs needs to be investigated in larger randomized controlled trials with comparable designs and outcomes.

Clinical and scientific implications
The findings in this thesis imply that muscle is an underappreciated organ that deserves recognition in counteracting detrimental clinical outcomes in older adults, especially during hospitalization. Measuring patients’ muscle status at admission to the hospital provides classification and allows to start monitoring muscle status over a longer period of time. Subsequently the general public needs to be educated about the advantages of healthy muscle status and how to maintain this at home. This will optimize adherence to lifestyle regimens and create sustainable interventions by making individuals aware of their own contribution to muscle health. Reduced numbers of readmissions and healthcare burden will likely result from these improvements.

Applying standard clinical tests during hospitalization may be too demanding and time consuming, or influenced by patient-related factors like hydration status, fatigue, immobilization and pain. A specific example is the floor effect in measurements of gait speed in bedbound patients. To overcome the obstacles posed by the hospital setting in diagnosing and preventing poor muscle status, some solutions are at hand; instrumented measurements could help facilitate future clinical diagnostics and provide alarm signals on inactivity and malnutrition during hospitalization. An example of a comprehensive application of instrumented measurements is creating smart systems, that may include components of continuous remote monitoring and controlling, self-management by feedback systems and automated measurements. Applying smart systems in the hospital could be a solution to time constrains and to physical limitations of older patients. Continuous measurements could increase reliability, and self-management would allow patients to perform the tests at their preferred times. For example, such a system could measure the time it takes for a patient to transfer every time he or she gets up from the bed. Information regarding the time, balance and frequency could remotely inform clinicians to guide discharge planning in addition to providing feedback to the patient. So far accelerometers in the hospital are only applied in research settings, mostly to evaluate and/or stimulate the amount of mobility throughout hospitalization, and instrumented tests or more comprehensive smart systems are rare in the hospital setting. Applications are being designed and validated at a fast rate and will likely be implemented in hospitals of the future.

Finally, prevention of muscle deterioration starting already from the third decade of life onwards will have a much greater long-term impact on societal health. Preventative therapies for younger adults have shown some positive results, yet evidence is scarce. The focus of preventative healthcare is shifting more and more towards lifestyle
medicine. An example of an intervention targeting the lifestyle of adults is PreventIT\textsuperscript{501}, using technology to facilitate the activity program. This program promotes awareness of the importance of muscle status before old age and changes lifestyle before apparent impairments arise. It applies technology to determine risk of poor muscle status and motivate behavior change. I hope that in a few years my medical suitcase, besides a stethoscope and sphygmomanometer, will contain a smart handheld device that allows me to measure muscle status in all my patients, young and old, to provide optimal healthcare.

**Conclusion**

In conclusion, this thesis obtained insights about the importance of preventing poor muscle status in older adults during hospitalization and identified a lack of knowledge and appropriate diagnostics in clinical practice. Creating awareness among clinicians and researchers as well as the general public about determinants and consequences of poor muscle status will improve prevention and treatment. Optimal healthcare to acutely or electively admitted patients, with lower cognitive function, inflammation or metabolic syndrome includes a focus on patients' muscle status before, during and after hospitalization. Let us appreciate this important organ and get into action to improve muscle status.