NOURISH THE MUSCLE
Nutritional Supplementation in Sarcopenia
Chapter 1

GENERAL INTRODUCTION
Aging and Muscle loss

Worldwide, populations in higher and lower income countries alike, are aging at a rapid pace. In 2010, 8% of the world’s population was over 65 years, and by 2050, this is expected to double to approximately 16% (1). This represents a significant demographic shift and, as such, it represents vast opportunities to strengthen interventions and resources aimed to prolong mobility and independent vital living. Ideally, a longer lifespan would mean more vital, active years; however, more than 40% of all European adults between 50 and 74 years have at least one mobility impairment (2), and between 40-50% of adults 75 years and older worldwide are considered “disabled” in terms of mobility (3).

Fighting disability has always been one of the cornerstones of geriatric medicine. Recently, the focus has shifted towards identification of early stages of disability, and prevention of, or slowing its onset. The progressive and insidious muscle loss during aging is closely related to the impairments in physical function and mobility, which eventually can lead to disability and loss of independence (Figure 1) (4). As Rosenberg clearly stated ‘there is probably no decline in structure and function more dramatic than the decline in lean body mass or muscle mass over the decades of life’ (5). Adults lose about 3-8% muscle mass per decade after the age of 30 years, and this rate of loss hastens later in life (6-10). This also represents an adverse shift in body composition, where the loss of muscle is replaced by an increased fat mass (11), which results in a loss of the quality and function of the existing muscle. The shrinking muscle mass and quality contributes to a significant decline in muscle strength and physical function, although muscle strength deteriorates at a much more rapid pace than muscle mass loss (8, 12).

Sarcopenia

This age-related loss in muscle mass, strength and function is termed sarcopenia. Rosenberg coined the term in 1988, when he combined “sarx” meaning flesh, and “penia” meaning poverty (5). More recently, the term sarcopenia has been increasingly operationalized by several working groups (13-15). Although there is no consensus for harmonized definition of sarcopenia, including

![Figure 1: Sarcopenia: A life course model. Adapted from Sayer et al., 2008 (4)](image)
diagnostic criteria with clear cut-off values (16), these criteria are similar and overlap. They state that the identification of sarcopenia is based on the presence of low muscle mass in addition to concomitant low muscle strength and/or low physical performance. As of October 1, 2016, sarcopenia is recognized as an independent condition by its own International Classification of Disease (ICD-10-CM). This is an important step for the field and will result in increased interest and support from the medical community, as well as industry, to improve screening and treatment options for sarcopenia (17).

The consequences of sarcopenia are mainly impaired physical function and mobility, disability for basic activities of daily living, increased likelihood of falls, loss of independence, poorer quality of life, and increased risk of all-cause mortality (18-21). Because of the costs associated with caring for an individual with compromised physical function, sarcopenia has been linked to elevated healthcare costs (22). The condition of sarcopenia is abundantly present in community-dwelling older adults, and it is particularly a concern during periods of hospitalization or immobilization, malnutrition and many (chronic) diseases (10, 23, 24). Muscle mass accounts for between approximately 20% and 50% of body mass depending of age and gender (25) and is the main body’s reservoir of readily available amino acids. As such, muscle mass is also essential for other physiological functions, including glucose and insulin metabolism, cellular communication and protein storage and turnover (26).

Loss of muscle mass is associated with delayed recovery from illness, decreased immunity, slowed wound healing, and other morbidities (27). In cancer patients, sarcopenia is associated with higher incidence of toxicity during chemotherapy (28), post-operative complications (23) and poorer survival (29, 30).

**Sarcopenia and Obesity**

In parallel with the demographic shift of aging, the proportion of older adults with obesity is rapidly growing (31). A number of the obese older adults have concomitant high fat mass and low muscle mass, a condition coined ‘sarcopenic obesity’. Both the relative muscle mass (the ratio between muscle mass and body weight) and the muscle quality (both in terms of fat infiltration or fibrosis and the ratio force per unit muscle mass) are often impaired in sarcopenic obesity. These shifts in body composition lead to higher insulin resistance, a higher risk of the metabolic syndrome (32) and diabetes type II (11). Obesity not only adversely affects mobility due to increased body weight, but it also has a deleterious effect on muscle quality. This decline in muscle quality is itself an independent predictor for disability and mortality (33). Sarcopenia and obesity jointly contribute to accelerated loss of strength, walking speed, and functional capacity (34). Sarcopenia is also an independent and adverse prognostic factor for other morbidities in overweight or obese patients (35, 36).

**Sarcopenia and Frailty**

Sarcopenia partially overlaps with another emerging geriatric giant, frailty. Frailty has been described as the multidimensional syndrome characterized by decreased reserves and diminished resistance to stressors, which exposes effected individuals to an increased risk for negative health-related events including falls, poorer disability, hospitalisation and institutionalization, and mortality (37, 38). Multiple factors, physical, psychological, cognitive, and social, contribute to the development of frailty. Although definitions of both sarcopenia and frailty are still developing and currently show very little concordance (39), both concepts clearly overlap in their physical aspects.
The physical frailty phenotype and its physiological consequences have been explained by Walston and Fried as the ‘frailty cycle’ based on a relationship between sarcopenia and energy imbalance (Figure 2) (40). Thus, sarcopenia is often a major determinant of the physical frailty phenotype. Recently, Landi et al. (2015) proposed a conceptual model with sarcopenia as the central element of physical frailty, similar to other age-related degenerative conditions such as chronic heart failure (CHF) and chronic obstructive pulmonary disease (COPD (21). According to this proposed model, muscle is the measurable biological substrate for both physical frailty and sarcopenia. The clinical manifestations of physical frailty and sarcopenia, such as reduced gait speed, impaired chair-stand ability and balance can be assessed by objective functional measures, such as the Short Physical Performance Battery (SPPB) and the ability to walk 400m (41, 42). Although there are no consensus definitions for sarcopenia and physical frailty and the potentially different etiology, both have the impairment of physical function as the core condition (43) and thus essential for the quality of life of these vulnerable older adults.

Figure 2: The ‘Frailty Cycle’ as core of the physical frailty phenotype.
Adapted from Fried et al., 2001 (44)
Universal Screening Tool (MUST) (48), Subjective Global Assessment (SGA) (49), Short Nutritional Assessment Questionnaire (SNAQ) (50), and Nutritional Risk Screening-2002 (NRS-2002) (51) are being used to detect malnutrition. These screening tools combine similar domains, i.e. weight loss, body mass index (BMI), appetite loss and reduced nutritional intake. A recent meta-analysis by Cereda et al. (52) calculated a prevalence of malnutrition of 3.1% and risk of malnutrition of 26.5% among community-dwelling older adults using the MNA. The etiology of malnutrition among older adults is complex and related to several factors such as changes in the absorption and utilisation of nutrients, diseases, as well as loss of appetite and/or decreased food intake, often called anorexia of aging (53). Eventually, this inadequate overall nutrient and energy intake can lead to undernutrition or protein-energy malnutrition, or recently described as quantitative malnutrition (53). In the early stages of anorexia, however, there is an increased risk of qualitative or selective malnutrition, due to suboptimal intake of single nutrients, such as protein and vitamins (14). Furthermore, the majority of older adults at risk for malnutrition have a normal BMI, often with a mean BMI around 26 kg/m² (54, 55). Recent systematic reviews of dietary intake among community-dwelling adults found a suboptimal energy and macronutrient distribution (56) and multiple inadequacies in micronutrient intake, where the mean intakes of six were below adequate: vitamin D, thiamin, riboflavin, calcium, magnesium and selenium (57). These suboptimal diets contribute to the development of sarcopenia and frailty (and vice versa) and several negative health outcomes (58, 59).

It is difficult to prospectively study the relationship between low nutritional intake and frailty and/or sarcopenia, and thereby determining causal relationships. However, the evidence from population studies for a relationship between malnutrition and sarcopenia or frailty among older adults is strong (60-63). Fifty-three percent of participants defined as frail in the InCHIANTI study had lower nutritional intake than those who were defined as ‘not frail’: caloric intake lower than 21 Kcal/kg was associated with an almost 25% increase in the risk of developing frailty (64). Similarly, the KNHANES survey for sarcopenia showed a significant lower energy intake in Korean older adults with sarcopenia (65). In addition to energy intake, inadequate protein intake is a critical factor in the development of sarcopenia (66) and frailty (67). The recommended 0.8 g/kg/d for protein intake is challenged as sufficient for older adults for preventing frailty, muscle decline and disability (68-71). Consequently, the PROT-AGE and ESPEN expert groups working groups introduced the following recommendations: higher protein intake of 1.0-1.2 g/kg body weight for healthy maintenance of aging muscles and up to 1.2-1.5 g/kg body weight/day for older adults with acute or chronic disease (72, 73). Also several micronutrient deficiencies or inadequacies are associated with frailty and sarcopenia through pathways that are still not well-understood (61, 74). One obvious example is the association of a low 25-hydroxyvitamin D level with the frailty status (75) and functional outcomes such as less physical activity, increased rates of falls and nursing home admission (76-79).

Recently, an ESPEN working group presented new criteria for the diagnosis of malnutrition after the individuals at risk were identified by validated screening tools (45). The diagnosis of malnutrition should be based on either a low BMI (<18.5 kg/m²), or on the combined finding of weight loss (either >10% of habitual weight indefinite of time, or >5% over 3 months) together with either reduced BMI (<20 or <22 kg/m² in subjects younger and
older than 70 years, respectively) or a low FFMI using sex-specific cut-offs (<15 and <17 kg/m² in females and males, respectively). An important new aspect of this definition is the focus on body composition, particularly fat-free mass (including muscle mass), in addition to total body weight. This implies that muscle mass is an important and relevant indication of adequate dietary intake and nutritional status.

**Nutrition for human Muscle**

Adequate nutritional intake is essential for the maintenance of muscle mass, and thus slowing sarcopenia progression (80). There is a continuous synthesis and breakdown of muscle proteins, which mainly constitute the myofibrillar contractile proteins. In total, 1-2% of the muscle protein is renewed daily in normal physiological conditions. The net balance between synthesis and breakdown determines whether there is either maintenance of muscle mass (i.e. net balance is zero), hypertrophy (i.e. positive balance) or atrophy (i.e. negative balance). The strongest anabolic trigger to stimulate muscle protein synthesis is physical activity, and especially in the form of resistance exercise. Dietary protein intake also triggers muscle protein synthesis by providing the building blocks, i.e. essential amino acids, for the renewal of contractile proteins of the muscle filaments. An adequate intake of dietary protein, combined with physical exercise, is required to ensure sufficient postprandial muscle protein synthesis, and thereby maintaining and potentially increasing muscle mass.

Older adults, however, are at high risk for insufficient protein intake. Lower dietary intake of protein has been consistently associated with greater muscle mass loss in older adults (61, 66, 79). Therefore the recent recommendations for older adults propose to increase the protein intake to the range of 1.0 up to 1.5g/kg body weight/day (72, 73). Aging does not seem to influence basal muscle protein synthesis and muscle protein breakdown (81, 82), but older muscle has a blunted anabolic response to low doses of essential amino acids, a condition known as ‘anabolic resistance’ (83, 84). The impaired activation of postprandial muscle protein synthesis by essential amino acids and other anabolic stimuli (for example, leucine and insulin) results in muscle atrophy, which can eventually lead to sarcopenia (83-85).

In addition to increasing daily dietary protein intake, nutritional strategies to overcome this anabolic resistance have focused on providing high-quality protein distributed over the day with sufficient protein intake at each meal. Each meal should ensure the provision of an adequate amount of readily available essential amino acids (minimally 10-15g) and leucine (3g) to stimulate muscle protein synthesis in older adults (73, 80).

It has been shown that dietary provision of non-essential amino acids does not have an additional effect (86). The essential amino acid leucine is, next to a substrate for muscle protein synthesis, also an anabolic trigger by activating the signaling factor of mammalian target of rapamycin (mTOR) to activate this process (87). Older adults require higher intakes of leucine to activate muscle protein synthesis compared to younger adults (88, 89). The plasma leucine peak after a meal is directly associated with the level of stimulation (90). This higher rise in plasma concentrations of essential amino acids and especially leucine is essential to overcome the anabolic resistance (91, 92) and is even more important in conditions of inflammation, insulin resistance, oxidative stress and inactivity where the anabolic resistance is even more severe (93, 94).

Another aspect is the timing of protein intake and the distribution of protein meals throughout the day. Consumption of a suffi-
cient amount (25-30 g) of high quality protein divided evenly over three meals seems to stimulate 24-hour muscle protein synthesis more effectively than a skewed protein distribution (95), which is typical of a western diet (greatest protein intake at the evening meal). A recent cross-sectional study stated that consumption of multiple meals with adequate protein content is associated with lean mass and muscle performance (96). The amount of protein traditionally ingested at breakfast is between 5-10 g protein (97, 98) and could therefore be a target to increase the total muscle protein synthesis throughout the day. Additional protein ingestion before bed is another interesting approach to maximize the anabolic response in older adults (99).

Moreover, appropriate timing of protein ingestion around physical exercise may have a positive and synergistic effect on skeletal muscle protein synthesis that leads to an accrual of skeletal muscle mass (92, 100). Physical activity, especially resistance exercise, enhances the sensitivity of muscle to essential amino acids. Even though protein synthesis in the first hour after exercise is maximized, the sensitivity of the muscle to protein feeding is enhanced for up to 24 h after exercise (101). As such, increasing the availability of essential amino acids during this period results in a maximum benefit of this improved anabolic window (102).

For other nutrients such as vitamin D, the importance in muscle protein metabolism is slowly emerging. A recent meta-analysis found an overall positive effect of vitamin D supplementation on muscle strength and function (103). Since vitamin D deficiency is associated with low muscle mass (104) and insulin resistance among older adults (105), vitamin D might play a role in anabolic stimulation. It has been shown in mechanistic studies that vitamin D deficiency often coincides with a decreased response to amino acids (84), and insulin (85). In a recent report (106), vitamin D acted synergistically with leucine and insulin to stimulate muscle protein synthesis, likely through sensitizing their anabolic pathways. A daily intake of at least 800 IU/d vitamin D (60), as well as calcium intake of 1000 mg/d, in combination with an adequate protein intake, has been recommended for older adults to maintain musculoskeletal health (107).

**Nutritional Supplementation**

Improving the nutritional status among certain groups of older adults may help to prevent the development of sarcopenia (19, 27, 108) and frailty (38, 109). An ESPEN expert group recommends the use oral nutritional supplements for the frail elderly at risk of malnutrition to improve or maintain nutritional status (110). Supplementation with protein-energy medical drinks can improve the nutritional status in geriatric patients with acute and/or chronic illnesses, at home as well as in nursing homes and hospitals, but the effects on functional status and quality of life are uncertain due to limited data (110).

Targeted nutritional interventions for improving muscle mass, strength and function as part of a multimodal approach might be a promising strategy to support sarcopenic, frail and older patient groups. Protein supplementation can help to increase the daily protein intake of older adults to meet the current recommendation of at least 1.0 g/kg/d (72, 73). It has been shown that supplements that contain high quality protein mixtures (such as whey protein), and thus minimally 10-15g of essential amino acids including 3g of leucine, were able to stimulate muscle protein in healthy and sarcopenic older adults (88, 111). The timing of supplementation during the day, preferably in combination with physical exercise, needs attention to maximize the efficacy of the
intervention. Furthermore, the protein/amino acid supplementation should be combined with an adequate vitamin D intake to maintain serum 25-hydroxyvitamin D levels higher than 50 nmol/L (107, 109). Other nutrients that are deficient or inadequately present in diets of older adults with sarcopenia should also be considered to be supplemented.

**Aims**

1. The first aim of this thesis was to characterize (community-dwelling) older adults with sarcopenia and/or frailty and their nutritional status.

2. The second aim was to examine the effect of a specific nutritional supplement on nutritional status and muscle measures in community-dwelling older populations with sarcopenia and/or obesity. We hypothesized that providing a targeted, low caloric vitamin D and leucine-enriched whey protein medical nutrition drink in a timely bolus amount, would result in the accretion of muscle protein and improvements of muscle strength and function.

**Thesis Outline**

**Part I** of this thesis, chapter 2-4, provides insights into primarily community-dwelling older adults with sarcopenia and frailty and an assessment of their nutritional status and malnutrition. **Chapter 2** provides a systematic review and meta-analysis of studies that assessed both malnutrition and frailty in community-dwelling older adults. This chapter gives insights in the prevalence of malnutrition in frailty, and vice versa, and may give some perspective for the contribution of selective malnutrition and sarcopenia in frailty development. **Chapters 3 and 4** contain the results of observational studies (one longitudinal and one case-control cross-sectional study) that provide indications for nutritional needs that exist among older adults, in particular those with sarcopenia. In **chapter 3** we evaluated the predictive power of muscle measures and nutritional status upon hospital admission for survival and living situation three months after discharge. This chapter helps to strengthen the rational for preventive nutritional strategies to improve muscle mass and function before periods of vulnerability such as hospitalization. **Chapter 4** includes the results of a case-control study among community-dwelling adults with and without sarcopenia. We compared the nutritional status, body composition and lower quality of life of sarcopenic older adults with age and sex matched non-sarcopenic controls. Although the direction of the relationships is unknown due to the cross-sectional design, the study may also provide an indication that adults with sarcopenia have certain nutrient gaps that could be playing a role in both the development and progression of sarcopenia.

**Part II** of this thesis, chapter 5-7, presents the effects of specific nutritional interventions on nutritional status and muscle measures in older adults with sarcopenia and/or obesity. **Chapter 5** includes the results of a nutritional intervention study with a vitamin D and leucine-enriched whey protein medical nutritional drink on muscle measures among 380 sarcopenic older adults (the PROVIDE study). In the post-hoc analysis from the PROVIDE study in **chapter 6**, we assessed whether serum 25-hydroxyvitamin D concentrations and dietary protein intake of PROVIDE participants at baseline modifies the intervention effect. This will evaluate the relevance of the current recommendations for vitamin D status and protein intake for adults with sarcopenia, given their strong relationship with muscle parameters. In the final results chapter (**chapter 7**), another potential inter-
vention with the same supplement was explored in a study with older adults with obesity. Since the prevalence of obesity in frail and sarcopenic older adults raise, it is interesting to examine whether older adults with obesity consuming this supplement together with a low caloric diet and participating in a weight-loss exercise program, could preserve skeletal muscle mass better than an iso-caloric control group. In chapter 8, we discuss the concepts of each of the chapters and describe how they support and challenge the current body of literature.
REFERENCES chapter 1


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