Frailty and the role of nutrition in older people
A review of the current literature

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Abstract. Frailty and malnutrition are both highly prevalent in the older population and have therefore become principle topics in geriatric research. Frailty is of multifactorial origin and is regarded as a fundamental risk factor for deteriorating health status and disability in older people. It is estimated that prevalence rates for frailty and pre-frailty reach as high as 27% and 51%, respectively. The role of nutritional deficiency in the development of frailty was suggested long ago, however research conducted in this area is relatively recent. The critical role of micronutrients in this context suggests the need to improve the quality of food eaten by older people – not just the quantity. This review summarizes the recent literature on the nutritional pathways to frailty with particular focus on the effect of energy, protein and micronutrients. (www.actabiomedica.it)

Keywords: Frailty, nutrition, malnutrition, functionality, elderly, micronutrients, antioxidants

Introduction

Over the past century, the world has seen enormous changes, including a historically unprecedented decline in mortality and increase in population growth. This century will see a new set of demographic challenges such as the subsequent aging of populations in both developing and developed countries. The 20th century was the century of population growth; the 21st century will go into the history books as the century of aging (1). Since the increase of life expectancy at birth did not parallel health expectancy, the rise in morbidity of the aging population will increase the medical costs and the burden on national healthcare systems. Both health and ageing are social and cultural constructs in addition to being biologically determined. Cultural and political factors also influence the health of older people. One has also to recognize that the health of the older is influenced by events throughout the course of their lives (life course perspective). This life course perspective leads to important policy and strategy decisions. It is clearly possible (and indeed desirable) to improve the health status of women and men when they are old. Yet, a complementary approach to improving the health of older people would focus on appropriate interventions from a much earlier age in order to prevent frailty, which is now seen as a multi-system disorder and one of the central geriatric syndromes. The operationalization of the frailty syndrome by Fried and Rockwood has to be regarded a “breakthrough” as a scientific issue (2-4). Frailty can be triggered by multiple pathophysiological processes such as malnutrition, hormonal dysbalances, chronic inflammation and multimorbidity. Frailty often leads to deterioration of health status, immobilization, disability and death and is particularly characterized by a reduced functional reserve and increased vulnerability to internal and external stressors (4). Frailty imposes therefore an increased risk on older people to recover inadequately from even minor events such as gastroenteritis or change of residence. An overview on the influencing factors on frailty or frailty-related parameters proposed is given in Table 1. Due to the diversity of parameters affecting the development of frailty, the
term “frailty puzzle” has been coined (6). Recognition and treatment of the causes for frailty and the frailty syndrome itself represent a key approach to improving the care for older people, particularly as frailty is highly prevalent in this population (7, 8). A recent publication implementing Fried’s criteria identified prevalence rates in various European countries ranging from 6% to 27% for frailty and from 35% to 51% for pre-frailty in persons above age 65 (9). Such high prevalence rates qualify for the term “epidemic”. Malnutrition of both macro- and micronutrients has been identified as an important risk factor for the development and severity progression of frailty in older people (10). This review aims at summarizing the recent literature on the nutritional links to frailty, frailty components and frailty-related parameters such as low muscle strength and low walking speed. Data on the prevalence of inadequate nutritional intake among older people and its association with frailty will be examined. The influence of energy and protein intake and particularly the role of micronutrients such as vitamins, antioxidants and trace elements will be discussed in the light of the most relevant publications.

### Frequency of inadequate nutritional intake among older people

Although food intake declines with aging which is possibly due to lower caloric requirement to maintain reduced lean body mass, inadequately low nutritional intake is frequently observed among older people, especially in those with increased care needs (11). The U.S. National Health and Nutrition Examination Survey (NHANES III) identified low energy and nutrient intake in up to 21% of the free-living older study population (12). The InCHIANTI study (Invecchiare in Chianti/Aging in the Chianti area, Italy) which examined nutritional status and nutrient intake in the general population including old and very old people, found a strong age-dependency of low energy, protein and micronutrient intake (13). Study participants older than 85 years had the lowest dietary intake of any examined nutrient which was in many cases below official recommendations. Twenty-nine percent of women and 38% of men in this age group did not meet their recommended protein intake. This proportion was even higher for some vitamins and trace ele-
Frailty and the role of nutrition in older people

Recent studies on nursing home residents found an even higher prevalence of poor nutrient intake. Inadequate energy intake was identified in 60% of the examined population, and inadequate micronutrient intake of vitamin E, vitamin B₆, folate, magnesium and zinc in 70% (15, 16). Although inadequate nutritional intake may be temporary and does not necessarily equal overt malnutrition or nutritional risk, similar findings were obtained when screening tools suitable for the older population such as the Mini Nutritional Assessment (MNA®) were applied in the nursing home setting. Kulnik et al. found that 38% of nursing home residents were malnourished, while another 48% were assessed as “at risk” of malnutrition (17). Wikby et al. reported 20% of nursing home residents to be malnourished and an additional 50% to be “at risk” (18).

Data on dietary intake in hospitalized older patients is rather scarce, which may be due to the shorter length of stay in hospitals compared to long-term care units and the time-consuming character of most methods which directly measure dietary intake (19). A recent study from the UK revealed inadequate food consumption, defined as having eaten less than three-quarters of the served dishes, in 67% of geriatric acute care patients (20). These findings should be interpreted considering the growing evidence that older people hospitalized for acute disease may require a higher protein intake to maintain a positive nitrogen balance than previously assumed and officially recommended in healthy older people (21).

Association of inadequate nutritional intake with frailty

If frailty in older people is promoted by poor nutritional intake, an association between these entities must be confirmed in observational studies. The majority of data on this topic have been derived from the aforementioned Italian InCHIANTI study and the U.S. Women’s Health and Aging Study (WHAS) which have systematically examined the relationship between nutritional status and frailty in large, longitudinal studies. Bartali and colleagues established a link between deficient nutritional intake and the frailty syndrome based on InCHIANTI study data implementing Fried’s criteria (10). Twenty percent of the InCHIANTI population was frail and out of those who were frail more than 53% showed deficient intake of at least one out of nine examined nutrients. About one third of the frail persons had an inadequate intake of more than three nutrients. An energy intake of less than 21 kcal/kg body weight/day was strongly associated with being frail. This observation was also valid for some micronutrients even independently from energy intake. The odds ratio for being frail associated with having three or more nutrient deficiencies compared to two deficiencies or less was 2.12. Based on data from the WHAS, Semba and colleagues identified low serum micronutrient concentrations as frailty predictors (22). At baseline, one third of the study participants were frail with significantly lower serum concentrations of numerous micronutrients (vitamin E, vitamin D, selenium, zinc) as compared to their non-frail peers. In the course of regular follow-up examinations about one third of the non-frail study participants became frail. Low micronutrient concentrations in non-frail persons at baseline were identified as an independent risk factor for becoming frail during the follow-up period. Also, the number of nutritional deficiencies was associated with an increased risk of becoming frail. Thus, as exemplified by the two mentioned studies, inadequate intake of energy and low serum concentrations of micronutrients have been associated with an increased prevalence of frailty and an increased risk of becoming frail in the future.

The role of protein in frailty

Several studies have established a link between insufficient dietary protein intake and low serum protein concentrations to frailty or frailty-related parameters of functionality in older people. In community-dwelling older people examined by the U.S. Health, Aging and
Body Composition Study (Health-ABC), Houston and colleagues demonstrated that low dietary protein intake was associated with loss of lean body mass (i.e. muscle mass) as measured by dual energy x-ray absorptiometry (DEXA) (23). All participants in the Health-ABC study lost muscle mass during the three-year follow-up period, but those with lowest protein intake at baseline (0.7 g/kg body weight/day) lost more than 40% more muscle mass than those with highest protein intake (1.1 g/kg body weight/day). Continuing loss of muscle mass eventually leads to sarcopenia which has been termed “nutritional frailty” to clarify the close interrelationship between poor nutritional status, loss of muscle mass and muscle strength, and functional decline (24). It was furthermore demonstrated on Health-ABC study data that lower serum albumin concentrations, even within the normal range, was associated with greater loss of muscle mass in a five-year follow-up (25). Unfortunately, no functional parameters were included to examine the implication of muscle mass loss on physical function in older persons.

Kwon and colleagues examined serum albumin and vitamin D, which are physiologically interconnected in muscle function and metabolism, and their association with physical performance among community-dwelling older Japanese (26, 27). Study participants with isolated deficiencies of either albumin or vitamin D had poor muscle strength as assessed by knee-extension power and hand-grip strength (one of Fried’s criteria) and impaired balance capability as assessed by the timed up-and-go test and functional reach. Even worse functionality, though, was found in persons with deficient serum concentrations of both albumin and vitamin D. These results illustrate the supposed synergistic effect of protein and vitamin D on muscle strength, which is of particular interest with regard to the high prevalence of vitamin D deficiency in the older population (28, 29). Serum albumin was found to be a predictor of future loss of muscle strength by Schalk and colleagues from the Longitudinal Aging Study Amsterdam (30). Even at baseline of this study, lower albumin values (<43 g/l) were associated with decreased muscle strength as measured by hand-grip strength. In a three-year follow-up examination, lower baseline serum albumin levels were significantly associated with an increased loss of muscle strength. Notably, such “lower” albumin levels were still higher than commonly reported cut-off values between 35 and 38 g/l which might emphasize the role of serum albumin as an early marker of muscle strength decline (30).

The role of micronutrients in frailty

The association between frailty and micronutrients, particularly those with antioxidative capacity, has come into research focus during the last years. “Oxidative stress” caused by free radicals is considered a major damaging influence on macromolecules (enzymes, lipids, DNA), a contributor to aging at the cellular level and an influencing factor on disability and mortality in older people (31-36). Many vitamins have antioxidative capacity, e.g. the vitamins A (retinol), C (ascorbate), D (cholecalciferol) and E (tocopherol group). Carotenoids constitute another group of antioxidants and comprise vitamin precursors and vitamin-like molecules like $\beta$-carotene, $\alpha$-carotene, lycopene, lutein and several more which are of utmost importance to scavenging free radicals (36). The main food source for carotenoids is fresh fruits and vegetables. Carotenoid serum concentrations are regarded the most valid markers of such intake (37). Some trace elements, too, like selenium bear antioxidative capacity after integration into proteins (selenoenzymes) where selenium constitutes the active centre. Zinc, another trace element, is involved in immune function and wound healing which are highly relevant attributes particularly at an advanced age (38). In some cases the physiological processes responsible for the protective effect of antioxidants is being uncovered. With regard to selenium, it was hypothesized that IL-6 takes the role of a mediator between selenium and muscle strength via the nuclear factor kappa-B (NF-$\kappa$B). Thereby higher selenium levels lead to a decreased concentration in NF-$\kappa$B which then results in a downregulation of IL-6, which has been shown to be related to muscle weakness and sarcopenia (42, 43). A similar pathway has been suggested for carotenoids (36). In other cases the pathways leading from micronutrient deficiencies to frailty and further on to disability and death are not yet fully explained.

Table 2 summarizes the available studies on micronutrient intake or micronutrient blood levels with
### Table 2. Overview on studies on the association of micronutrients with frailty or related parameters

<table>
<thead>
<tr>
<th>Original Study</th>
<th>Author, year</th>
<th>Examined micronutrients</th>
<th>Examined parameter (frailty, function, outcome)</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>WHAS</td>
<td>Semba et al., 2009 (91)</td>
<td>Vitamin D</td>
<td>Mortality</td>
<td>Low levels of vitamin D are associated with an increased risk for all-cause mortality</td>
</tr>
<tr>
<td>WHAS</td>
<td>Alipanah et al., 2009 (92)</td>
<td>Carotenoids</td>
<td>Walking speed</td>
<td>Low serum carotenoids are associated with decline in walking speed</td>
</tr>
<tr>
<td>WHAS</td>
<td>Beck et al., 2007 (42)</td>
<td>Selenium</td>
<td>Hand-grip strength (HGS)</td>
<td>Low serum selenium levels associated with poor HGS</td>
</tr>
<tr>
<td>WHAS</td>
<td>Semba et al., 2007 (33)</td>
<td>Carotenoids</td>
<td>Walking speed</td>
<td>Low serum carotenoids predict walking disability</td>
</tr>
<tr>
<td>WHAS</td>
<td>Michelon et al., 2006 (39)</td>
<td>Vitamin E, vitamin D, carotenoids, selenium, zinc</td>
<td>Frailty</td>
<td>Association between serum micronutrient levels and frailty</td>
</tr>
<tr>
<td>WHAS</td>
<td>Semba et al., 2006 (22)</td>
<td>Carotenoids, vitamin D, and others</td>
<td>Frailty</td>
<td>Low serum micronutrient levels associated with increased frailty risk. Frailty risk increases with number of deficiencies.</td>
</tr>
<tr>
<td>WHAS</td>
<td>Bartali et al., 2006 (10)</td>
<td>Vitamins B6, vitamin B12, selenium</td>
<td>Disability</td>
<td>Low serum micronutrient levels predictive for disability (defined by ADL function)</td>
</tr>
<tr>
<td>WHAS</td>
<td>Ray et al., 2006 (41)</td>
<td>Carotenoids, selenium</td>
<td>All-cause mortality</td>
<td>Low serum micronutrients predict mortality</td>
</tr>
<tr>
<td>CVHS#</td>
<td>Walston et al., 2002 (40)</td>
<td>Carotenoids, selenium</td>
<td>IL-6, mortality</td>
<td>Higher serum micronutrient levels associated with lower IL-6 levels and lower mortality</td>
</tr>
<tr>
<td>InCHIANTI</td>
<td>Shardell et al., 2009 (94)</td>
<td>Vitamin D</td>
<td>Frailty</td>
<td>Low vitamin D levels increase frailty risk in men, not women</td>
</tr>
<tr>
<td>InCHIANTI</td>
<td>Semba et al., 2009 (90)</td>
<td>Vitamin D</td>
<td>Mortality</td>
<td>Low serum levels of vitamin D are associated with an increased risk for all-cause mortality</td>
</tr>
<tr>
<td>InCHIANTI</td>
<td>Bartali et al., 2008 (45)</td>
<td>Vitamin E</td>
<td>Short physical performance battery (SPPB)</td>
<td>Low serum vitamin E levels associated with decline in SPPB functions</td>
</tr>
<tr>
<td>InCHIANTI</td>
<td>Lauretani et al., 2008 (47)</td>
<td>Carotenoids</td>
<td>Hip strength (HS), Knee-extension strength (KES), HGS</td>
<td>Low plasma carotenoids associated with decline in muscle strength</td>
</tr>
<tr>
<td>InCHIANTI</td>
<td>Lauretani et al., 2008 (37)</td>
<td>Carotenoids</td>
<td>Walking speed</td>
<td>Higher serum carotenoids associated with lower risk of developing walking disability</td>
</tr>
<tr>
<td>InCHIANTI</td>
<td>Lauretani et al., 2008 (48)</td>
<td>Carotenoids</td>
<td>Mortality</td>
<td>Low plasma carotenoids associated with increased mortality</td>
</tr>
<tr>
<td>InCHIANTI</td>
<td>Lauretani et al., 2007 (49)</td>
<td>Selenium</td>
<td>HGS, KES, HS</td>
<td>Low plasma selenium associated with muscle strength</td>
</tr>
<tr>
<td>InCHIANTI</td>
<td>Lauretani et al., 2008 (50)</td>
<td>Selenium</td>
<td>Mortality</td>
<td>Low plasma selenium associated with increased mortality</td>
</tr>
<tr>
<td>InCHIANTI</td>
<td>Houston et al., 2007 (93)</td>
<td>Vitamin D</td>
<td>SPPB</td>
<td>Low vitamin D levels are associated with poor physical performance</td>
</tr>
<tr>
<td>InCHIANTI</td>
<td>Ble et al., 2006 (44)</td>
<td>Vitamin E</td>
<td>Frailty</td>
<td>Association between low plasma vitamin E levels and frailty</td>
</tr>
<tr>
<td>InCHIANTI</td>
<td>Cesari et al., 2004 (46)</td>
<td>Vitamin C, α-tocopherol, γ-tocopherol, β-carotene</td>
<td>KES, SPPB</td>
<td>Higher dietary micronutrient intake associated with higher KES and SPPB</td>
</tr>
</tbody>
</table>

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frailty, related physical parameters and outcome parameters such as mortality. Again, the majority of data comes from the WHAS and the InChianti study. Although the WHAS lacks data on men and some of the reported publications did not examine frailty per se but more or less isolated performance parameters or even disability, which may be regarded the state “beyond” frailty, these findings give a hint towards the impact of micronutrient deficiencies on physical well-being, functionality and even mortality in older people.

Other nutrition-related causes for frailty

From WHAS data it was shown that chewing and swallowing problems and use of dentures influence dietary intake and represented a risk factor for malnutrition, frailty and mortality (51). Denture users had significantly lower serum levels of carotenoids and vitamin D. Denture use was particularly high among frail study participants and an increased five-year mortality risk was observed for those denture users who complained about swallowing and chewing difficulties. Given the high prevalence of denture use among older people, the maintenance of masticatory function and oral health seems crucial to uphold the ability to adequate and satisfactory nutrition.

Conclusion

Inadequate nutritional intake is frequent among older people and related to increasing dependence and care needs. The association between poor nutritional intake and frailty was demonstrated in numerous recent studies. Not only have energy and protein intake been linked to frailty and frailty-related parameters. Particularly the role of micronutrients in the development of frailty has been highlighted in recent publications. Micronutrient intake has been found to be associated with frailty or related parameters of physical functioning, sometimes even independent from energy intake. In conclusion, macro- as well as micromalnutrition may be regarded as one of the key factors contributing to the development and aggravation of frailty. An increased perception of the role of micronutrients in this process may lead to further improvements in the quality of food eaten by older people - not just the quantity of food. In clinical practice and as part of the management of aging it should therefore be recommended to use a suitable tool for routine screening of nutritional risks. Consequently, the goal will be to raise the general dietary intake of high-quality food to provide sufficiently both macro- and micronutrients.

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