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Micronutrients and sarcopenia: current perspectives

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Sarcopenia, a skeletal muscle disorder that is characterised by loss of muscle strength and mass, is common in older populations and associated with poorer health outcomes. Although the individual and economic costs of sarcopenia are widely recognised, current understanding of its pathophysiology is incomplete, limiting efforts to translate research evidence into effective preventive and treatment strategies. While nutrition is a key field of sarcopenia research, the role of differences in habitual diets, and the effectiveness of dietary change as a prevention or treatment strategy, is uncertain. There is a growing evidence base that links low micronutrient intakes to sarcopenia risk and/or its components (low muscle strength and mass, impaired physical performance), although there remain many gaps in understanding. There is some consistency in findings across studies highlighting potential roles for antioxidant nutrients, B vitamins and magnesium; however, the evidence is largely observational and from cross-sectional studies, often describing associations with different muscle outcomes. As low intakes of some micronutrients are common in older populations, there is a need for new research, particularly from well-characterised prospective cohorts, to improve the understanding of their role and importance in the aetiology of sarcopenia and to generate the evidence needed to inform dietary guidelines to promote muscle health.

Sarcopenia: Muscle: Ageing: Micronutrient

Sarcopenia is a progressive skeletal muscle disorder that is characterised by loss of muscle strength and mass[1]. First described by Rosenberg in 1989, it has generated huge research interest in the decades since[1–3] leading to progress in its definition and diagnosis, using agreed thresholds for low muscle strength and mass, and impairments in physical performance[4]. Sarcopenia is now recognised as an independent condition; its International Classification of Diseases-10 code was assigned in 2016[2].

Sarcopenia is common, particularly in older populations and among individuals with co-morbidities such as CVD and dementia[5], and is associated with poor health outcomes, that include frailty[2], falls[6] and greater mortality[1]. Therefore, apart from the burden on affected individuals, the associated economic costs are significant. For example, a recent estimate of the annual excess care costs in the UK associated with muscle weakness was £2·5 billion[7]. However, current understanding of the pathophysiology of sarcopenia is incomplete, limiting opportunity to translate research evidence into effective preventive and treatment strategies. There are currently no licensed pharmacological

Abbreviation: ROS, reactive oxygen species.
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treatments for sarcopenia[1] and exercise and dietary interventions are proposed as main options in clinical management[8]. The benefits of progressive resistance exercise training, to increase muscle strength and mass, are clearly established, either alone[9] or in combination with nutritional supplementation[10]. In comparison, although nutrition was shown to be a key field of research in a recent bibliometric analysis of the most highly cited papers on sarcopenia[3], the evidence that links differences in habitual diets to the risk of development of sarcopenia[11], or showing the effectiveness of dietary change as a prevention or treatment strategy, is incomplete[12]. There is a need for new research to improve the understanding of the influences of diet and nutrition on the losses of muscle strength and mass that lead to sarcopenia[13].

Nutrition and sarcopenia

Sarcopenia has multifactorial causes that impact the homoeostasis of skeletal muscle (summarised in Fig. 1)[1]. Beyond the effects of overt malnutrition, that lead to losses of body weight and muscle mass, more modest differences in nutrient intake and status have the potential to influence a number of the proposed mechanisms that underlie muscle loss.

The most intensively researched aspect of nutrition in relation to its effects on muscle strength and mass is protein/amino acids[3], both to address the need for amino acids for protein synthesis as well as recognition of a blunted anabolic response to protein consumption in older age, such that protein requirements may need to be higher in older populations[11,12]. There is now a large body of evidence from intervention studies that evaluate the effects of protein supplementation on muscle strength and mass, although to date, findings have been mixed[14]. While there has also been significant interest in the role of vitamin D and its influence on muscle health, with a range of studies investigating the effects of supplementation – both alone and in combination with protein and/or exercise training[15,16] – evidence on other micronutrients is much more limited. However, as a number of mechanistic pathways, including inflammation and oxidative stress[1], point to the importance of micronutrients, a much clearer understanding of

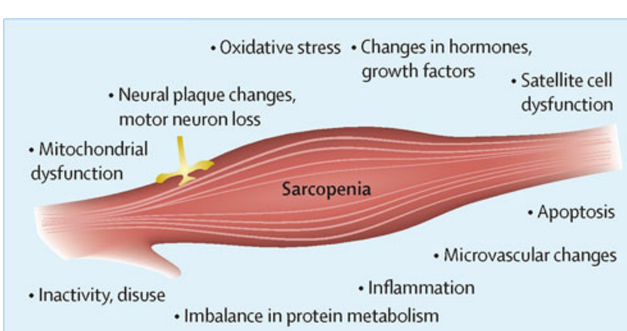

Fig. 1. Multifactorial causes of sarcopenia. From Cruz Jentoft and Sayer[1].

their roles in the aetiology of sarcopenia is needed. This review considers current evidence on the effects of micronutrients on sarcopenia and its components (muscle mass, strength and physical performance) and examines, in the context of contemporary data on the habitual intakes of older populations, the implications of this evidence for muscle health.

Antioxidant nutrients

Oxidative stress is thought to be a key contributor to skeletal muscle decline[17] with markers of oxidative damage, such as serum protein carbonyls, shown to predict impairment in physical function[18]. The high level of metabolic activity in skeletal muscle generates reactive oxygen species (ROS), making it susceptible to oxidative stress[19]. Excess accumulation of ROS results in damage to biomolecules in muscle (DNA and proteins) and, via effects on signalling pathways, impacts on inflammation. However, ROS have dual roles and, at physiological levels, are also needed for normal muscle function[20]. ROS production is normally balanced both by the actions of endogenous antioxidant defence systems, such as the enzymes superoxide dismutase and glutathione peroxidase, and by exogenous (dietary) antioxidants, which prevent excess accumulation[19]. This has focused attention on a range of dietary components that have antioxidant effects, in order to understand the extent to which low antioxidant intakes and status may be involved in the aetiology of sarcopenia, and the potential for benefits of dietary antioxidant supplementation as part of strategies to promote muscle health.

Early evidence from the InCHIANTI (Invecchiare in Chianti) and the Women's Health and Ageing Study cohorts, published more than a decade ago, provided key supportive evidence for the role of dietary antioxidants. For example, in cross-sectional studies, lower selenium[21], carotenoid[22] and vitamin E[22] status (blood concentrations) were associated with lower muscle strength; a later cross-sectional study of an older population of Japanese women, showed a positive association between vitamin C status and muscle strength and physical performance[23]. More recently, positive indication of dietary antioxidant effects has come from analysis of cross-sectional data from women aged 18–79 years in the TwinsUK cohort: greater leg explosive power was found in association with higher intakes of vitamin C and total carotenoids, although no association was found with vitamin E intakes[24]. Cross-sectional studies of selenium intakes and status have shown positive associations with muscle mass and physical performance, although evidence is limited and the findings are mixed[25]. However, given the prevalence of low selenium intakes in the UK population shown in the National Diet and Nutrition Survey (39 % men and 76 % women aged 75 years and over have intakes below the lower reference nutrient intake)[26], further information is needed.

Importantly, follow-up studies have provided prospective evidence that indicates protective effects of antioxidant nutrients, with higher vitamin E[27] and carotenoid[28] status at baseline shown to predict smaller declines in physical function. However, despite the positive messages from these observational studies, there has been less progress in the period since the early data were published to inform understanding of the role and importance of antioxidant nutrients for muscle health. New prospective data on antioxidant intakes (vitamins C and E, total and individual carotenoids) from a 12-year follow-up of the Framingham Offspring cohort, by Sahni and colleagues therefore make an important addition to the evidence base[29]. In this study, associations between antioxidant intakes and annualised change in grip strength and gait speed were examined. In adjusted models (taking account of age, sex, body size, physical activity, energy intake, current smoking, multivitamin supplement use and baseline grip strength), higher intakes of total carotenoids, lycopene and lutein + zeaxanthin were associated with greater grip strength; higher intakes of total and all individual carotenoids assessed, and vitamin E, were associated with faster gait speed, although there were no associations with vitamin C intake. However, while this study provides new evidence that appears consistent with earlier data, the authors did not confirm the findings when they analysed data from a comparison cohort (Cardiovascular Health Study). In The Cardiovascular Health Study, grip strength and gait speed were compared with vitamin C and β-carotene intakes: with the exception of an association between vitamin C intake and grip strength, there were no other associations[29]. The discrepancy in findings may be due to methodological differences between studies, particularly age differences between cohorts[30], but it highlights the need for further prospective evidence.

There is little intervention evidence to describe the effects of antioxidant supplementation on sarcopenia[20]. Importantly, there is some debate about the need for more trials[30,31]; as ROS have physiological as well as pathological roles, supplementation with dietary antioxidants may be unlikely to be effective at slowing age-related losses in muscle mass and function[31], and there are also concerns about the effects of long-term supplementation[20]. The existing evidence is patchy and inconsistent; for example, in trials of supplementation of older individuals with vitamins C and E in combination with exercise training, one showed there was no effect of daily supplementation (1000 mg vitamin C, 600 mg vitamin E) on strength gains over 6 months[32], with suggestion from another trial, that adaptations to training (muscle thickness) were blunted as a result of supplementation (1000 mg vitamin C, 235 mg vitamin E)[33]. Although these were short-term trials, longer duration of supplementation with vitamins C and E was also shown to be ineffective in a recent observational study: in a community-dwelling population, studied over a 5-year period, there were no differences in muscle strength (handgrip) or in incidence of low strength, when comparing supplement users with non-supplement users[34]. The findings for selenium appear similar; for example, in a 4-year trial of supplementation in an older population (provided as organic selenium yeast in combination with coenzyme Q10) there were no differences in physical performance, assessed using the SF-36 questionnaire when comparing the supplemented and placebo groups[35]. The overall message from this limited evidence base is that simple supplementation approaches, providing individual antioxidants, are not effective at improving muscle health.

Other approaches to understand the effects of dietary antioxidants on muscle health outcomes are needed. In particular, a consideration of the role of whole foods that are naturally high in antioxidants, and the potential for whole-diet approaches to promote their consumption, may be a more promising strategy[30]. In this context, it is a concern that fruit and vegetable consumption in older populations may be low; for example, recent data from the National Diet and Nutrition Survey show that less than one in five adults aged 75 years and over meet the dietary recommendation to consume five or more portions of fruit and vegetables each day[26]. Overall, despite the potential importance of low antioxidant intakes as a determinant of sarcopenia, current evidence is insufficient to inform dietary strategies to protect muscle health.

Vitamin D

There is a known link between proximal muscle weakness and vitamin D deficiency and there has been intense interest in the opportunity to use vitamin D supplementation as part of strategies to prevent and treat sarcopenia. The mechanisms that explain the effects of vitamin D are not fully understood, but may be mediated by the vitamin D receptor, via effects on gene transcription and protein synthesis as well as it having a potential anti-inflammatory role[36,37]. Much of the research on vitamin D and muscle health has been experimental, with many intervention trials carried out, often in combination with protein, and with/without exercise training[38]. In comparison, despite global concerns about the prevalence of low vitamin D status across older populations[39], there is less evidence to inform understanding of the role of habitual dietary intakes and the importance of observed differences in status in the aetiology of sarcopenia. Some population studies have linked lower vitamin D status to lower muscle strength and to declines in strength. For example, in an early paper from the Longitudinal Ageing Study Amsterdam, participants with lower serum concentration of vitamin D at baseline were more likely to experience loss of muscle strength and mass during the 3-year follow-up (adjusted OR for low status (25-hydroxyvitamin D < 25 nmol/l) 2·57 (1·40–4·70) and 2·14 (0·73–6·33) respectively), when compared with the group with adequate status (50+ nmol/l)[40]. However, the observational evidence published since has been more mixed, with an absence of associations with vitamin D status and muscle outcomes also reported in some studies[12].

The sizeable body of intervention evidence has been evaluated in a number of systematic reviews and meta-analyses. However, depending on the selection of studies, there are differences in the conclusions reached. For example, an analysis of pooled data from twenty-nine randomised controlled trials, published in 2014, showed that vitamin D supplementation had a small

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but significant positive effect on muscle strength[41], whereas reviews of studies of older populations published more recently, have not confirmed this[42–44]. Comparable inconsistencies have also been described for measures of physical performance, such as the Timed-Up-and-Go test, in supplementation studies – with both positive[43] and negative[42] findings reported. In part, this may be due to differences in the populations studied and, particularly, due to differences in the vitamin D status of participants at baseline. Some reviews have concluded that effects are more evident among participants with low status at baseline[41,42,45], as might be expected, although evidence of this differential response has not been confirmed by other authors[43], including a recent 4-month trial of supplementation of a population of vitamin D-insufficient men and women – no differences in muscle strength were found in the supplemented group[46]. There may be benefits of vitamin D supplementation when combined with protein[15] and/or exercise training[47], but whether there are benefits of vitamin D supplementation alone to prevent or treat sarcopenia remains unclear.

B vitamins

The role of B vitamins in the aetiology of sarcopenia has not been studied extensively although given their involvement, both direct and indirect, in an array of relevant biological processes, their contribution could be significant[48]. In a review of the possible influences of B vitamins on sarcopenia, Aytekin and colleagues highlight their involvement in energy and protein metabolism and the known links between deficiencies and neuromuscular effects[48]. For example, deficiencies of vitamins B_1 (thiamine) and B_3 (niacin) are associated with deficits that include muscle weakness and fatigue, whereas vitamin B_6 (pyridoxine) deficiency is associated with effects on the peripheral nervous system, and with loss of motor function[48]. However, in terms of the evidence base, perhaps the clearest indication of the potential role of B vitamins comes from studies of circulating homocysteine concentrations in relation to muscle mass and function. A number of studies link higher homocysteine concentrations to poorer outcomes, both in cross-sectional and longitudinal studies of older populations, showing associations with impairments in muscle strength[49,50] and physical performance[51,52]. While there are some inconsistencies across studies, particularly with respect to differences between men and women[53], the findings point to the importance of nutrients involved in one-carbon metabolism such as folate, B vitamins (B_6 and B_{12} (cobalamin)), methionine and choline. There is some observational evidence that is consistent with this possibility; for example, among older adults followed up over 3·5 years, higher intakes of vitamin B_6 intake were linked to a lower risk of impaired mobility[54], in older diabetic patients, serum folate concentration was correlated with muscle strength[55], and among older outpatients undergoing a comprehensive geriatric assessment, low serum vitamin B_{12} was associated with lower muscle strength and mass[56]. Furthermore, in the Maastricht Sarcopenia Study, sarcopenic older adults were found to have lower intakes of vitamin B_6 and folate, when compared with non-sarcopenic older adults[57] and in the UK Biobank study, higher intakes of folate and vitamin B_{12} were associated with a lower odds of sarcopenia[58]. This may be a concern for older populations; for example, UK data from adults aged 75 years and over in the National Diet and Nutrition Survey showed that 27 % of men and 23 % of women had serum folate concentrations below the threshold for possible deficiency (13 nmol/l); the prevalence of low vitamin B_{12} status (below 150 pmol/l threshold for deficiency) was 8 % in men and 7 % in women[26].

The observational data suggest that vitamin B supplementation should be effective at promoting muscle health. However, in a 2-year randomised controlled trial of vitamin B_{12} and folic acid supplementation with vitamin D_3 (B-PROOF), there were no differences in muscle strength or physical performance when compared with the placebo group (vitamin D_3 alone), although there was some indication of a positive effect on gait speed[59]. There may be a number of reasons to explain why the associations seen in observational studies were not translated into effects in this trial. One reason may be related to the challenges in interpreting and defining roles of individual B vitamins in dietary datasets in which they are highly correlated – for example, in a study of older women in the VITAL cohort, the range of coefficients for folate, methionine and the vitamins B_2 (riboflavin), B_6 and B_{12} ranged from 0·64 to 0·80[60]. In order to inform mechanistic understanding, new methods are therefore needed that enable consideration of independent nutrient effects. An example of this kind of novel approach was published recently by Behrouzi and colleagues; using Copula Graphical Models to evaluate combined data from four studies of older adults, they were able to describe direct and indirect nutrient associations with measures of physical function. These analyses showed that higher intakes of vitamin B_6 and folate were directly (positively) correlated with scores for the short physical performance battery, and that vitamins B_6 and B_{12} were correlated with scores for the chair rise test; there were no direct correlations with handgrip strength[61]. The ability to identify nutrient associations that are adjusted for the effects of other dietary variables within the same dataset is a major advantage, and may offer important new insights to improve understanding of the role and importance of B vitamins in the aetiology of sarcopenia.

Although relatively small at present, this growing evidence base indicates potential roles of B vitamins in the aetiology of sarcopenia. However, further data are needed to inform understanding of this potential, and the implications for muscle health.

Magnesium

Magnesium is involved in a wide range of biological processes and pathways that affect muscle function, such as transmembrane transport and energy metabolism, and is essential for muscle relaxation and contraction[25,62]. Although evidence is limited, there is significant interest in the effects of magnesium status and intakes on muscle health; in a systematic review of the role of minerals, published in 2018, van Dronkelaar and colleagues identified magnesium as one of the most promising to prevent and/or treat sarcopenia[25]. Higher intakes of magnesium have been shown to be positively correlated with appendicular muscle mass and change in appendicular muscle mass in a longitudinal study[63], and with fat-free mass[64–66] in cross-sectional studies. These associations were evident in younger and older adults, and in men and women, although no associations were found with serum magnesium concentration[64]. While there are fewer studies of functional outcomes, positive correlations with magnesium intake have been shown with muscle strength[67], including a recent analysis of cross-sectional data from UK Biobank, in which clear positive associations were described both in men and women[68]. Evidence relating magnesium intakes to diagnosed sarcopenia appears consistent with these findings on muscle mass and function, with a number of observational studies showing sarcopenic older adults to have lower magnesium intakes when compared with non-sarcopenic[57,69,70]. For example, in the UK Biobank cohort, the adjusted OR for sarcopenia (accounting for age, sex, deprivation and education) was 0·61 (95 % CI 0·50–0·74) for the highest third of magnesium intakes, when compared with the lowest[58].

These observational studies are mainly cross-sectional, but the consistency in findings across them highlights the potential importance of dietary magnesium as an influence on muscle health. This could be a concern as, in the recent analysis of UK data for adults aged 75 years and older in the National Diet and Nutrition Survey, 22 % of men and 27 % of women had intakes below the lower reference nutrient intake. At present, there is limited evidence on the effects of magnesium supplementation, although there is some indication of beneficial effects; for example, in a 12-week study of older women (supplemented with 300 mg/d) attending a fitness programme, Veronese and colleagues showed improvement in Short Physical Performance Battery (SPPB) scores in the treatment group, and with more marked effects apparent in participants with low dietary intakes[62]. However, the effects of supplementation in other studies (of younger populations) is mixed with both positive (combined with vitamin D)[71] as well as no[72] effects reported. Overall, the evidence is indicative of a positive role of magnesium as an influence on muscle health; given the evidence that low habitual intakes are common, further research is needed.

Diet quality and micronutrients

The observational evidence reviewed in preceding sections provides some indication of the benefits of higher intakes of antioxidant nutrients, B vitamins and magnesium for muscle health in older populations. There is also a growing evidence base for positive effects of other micronutrients that are not considered here, including calcium[25,58,69], potassium and other minerals[25,68]. However, the more limited intervention evidence, to test supplementation effects of individual micronutrients or combinations of them, is less consistent. There may be mechanistic reasons why the benefits of supplementation are less clear[31] but a particular concern is that dietary micronutrients are highly correlated[60], such that an observed pattern of diet that provides a high intake of one micronutrient is also likely to provide a high intake of another. This is a significant limitation in understanding the effects of many dietary components that challenges our ability to delineate their individual effects[61] and may be very relevant in understanding the links between micronutrients and muscle health. Thus, despite the mechanistic basis that links individual micronutrients to muscle outcomes, there is a possibility that some of the observational evidence that appears to describe associations with different micronutrients relates to similar axes of variation in the dietary data. High micronutrient intakes may be indicators of diets of higher ‘quality’, characterised by greater consumption of fruits, vegetables and whole-grain foods and lower consumption of highly processed foods, refined grains and added sugar, that are beneficial for muscle health.

There is now an established literature that links ‘healthier’ dietary patterns to positive effects on muscle mass and function[73,74]. Although there are differing definitions of healthy patterns across settings, there is significant overlap in terms of their core tenets[75], particularly the characteristic, greater, consumption of fruit and vegetables. But, importantly, apart from being more micronutrient-dense, such patterns also differ in other components that may be important for muscle health. Of particular relevance is their higher content of plant bioactives, such as polyphenols which have been shown to relate to a lower risk of decline in physical performance[76]; in addition, other aspects, such as differences in the overall inflammatory potential of the diet[77], and the relatively low consumption of ultra-processed foods[78] may also be important. While considering whole diets may not inform understanding of the causal mechanisms that link individual micronutrients to muscle health, it is likely to be essential to the interpretation of observational intake data and, importantly, should be considered in future intervention strategies.

Conclusions

Although there is a growing evidence base that links differences in micronutrient intake to sarcopenia risk and its components (muscle strength, mass and function), it is limited and incomplete. Current evidence is largely observational and varies in the muscle outcomes it has considered, which cannot be used interchangeably to inform understanding of micronutrient nutrition and its role in the aetiology of sarcopenia[12]. There is some consistency in findings across studies that highlight potential roles for antioxidant nutrients, B vitamins and

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magnesium, but the evidence is largely observational and from cross-sectional studies. As low intakes of some micronutrients are common in older populations, there is a need for new research, particularly from well-characterised prospective cohorts, to improve understanding of their role and importance in the aetiology of sarcopenia and to generate the evidence needed to inform dietary guidelines to promote muscle health[13].

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Authorship

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