Conference on 'Malnutrition matters'
Muscle wasting with age: a new challenge in nutritional care; part 2 – management

Nutrition and sarcopenia: evidence for an interaction

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Nutritional interventions that might influence sarcopenia, as indicated by literature reporting on sarcopenia *per se* as well as dynapenia and frailty, are reviewed in relation to potential physiological aetiological factors, i.e. inactivity, anabolic resistance, inflammation, acidosis and vitamin D deficiency. As sarcopenia occurs in physically active and presumably well-nourished populations, it is argued that a simple nutritional aetiology is unlikely and unequivocal evidence for any nutritional influence is extremely limited. Dietary protein is probably the most widely researched nutrient but only for frailty is there one study showing evidence of an aetiological influence and most intervention studies with protein or amino acids have proved ineffective with only a very few exceptions. Fish oil has been shown to attenuate anabolic resistance of muscle protein synthesis in one study. There is limited evidence for a protective influence of antioxidants and inducers of phase 2 proteins on sarcopenia, dynapenia and anabolic resistance in human and animal studies. Also fruit and vegetables may protect against acidosis-induced sarcopenia through their provision of dietary potassium. While severe vitamin D deficiency is associated with dynapenia and sarcopenia, the evidence for a beneficial influence of increasing vitamin D status above the severe deficiency level is limited and controversial, especially in men. On this basis there is insufficient evidence for any more specific nutritional advice than that contained in the general healthy lifestyle–healthy diet message: i.e. avoiding inactivity and low intakes of food energy and nutrients and maintain an active lifestyle with a diet providing a rich supply of fruit and vegetables and frequent oily fish.

Aging: Dynapenia: Inactivity: Anabolic resistance: Diet

In a recent consensus paper sarcopenia[1] was defined as the age-associated loss of skeletal muscle mass and function, a complex syndrome associated with muscle mass loss alone or in conjunction with increased fat mass. It was argued that although cachexia may be a component of sarcopenia, the two conditions are not the same. What was not discussed in this paper was the difference between sarcopenia and dynapenia which is important in terms of the clinical relevance of the condition. Thus Jansonn[2] points out that the data on the functional implications of sarcopenia are inconsistent, possibly because we do not always recognise the distinction between sarcopenia, loss of muscle mass and dynapenia and loss of muscle strength. These, he argues, are physiologically different with dynapenia the main predictor of functional impairment and/or physical disability, chronic disease and mortality risk, to the extent that research and clinical emphasis should be placed more on dynapenia than on sarcopenia. In fact this argument can, to some extent be extended to include frailty, a much more general term for a collection

of age-related disabilities which includes, to variable degrees, sarcopenia and dynapenia, but which does not have an internationally agreed definition. Here, although the primary focus is on nutrition and sarcopenia *per se*, given the limited extent of the literature, studies reporting on dynapenia and frailty are also reviewed.

Jansonn also highlights the importance of sarcopenic obesity, the condition in which not only is muscle mass replaced by adipose tissue, a widespread phenomenon, but where excess adiposity, resulting in overweight or obesity, coexists with weakness due to sarcopenia. Some studies suggest that approximately 15% of those with sarcopenia are also obese[2]. The importance of sarcopenic obesity, especially when the obesity is of the abdominal type, is that it links adiposity and sarcopenia mechanistically through inflammation deriving from the adiposity[3,4], and highlights the importance for elders of minimising the development of obesity especially of the abdominal type. The recent consensus statement[1] described the causes of sarcopenia as multifactorial, including disuse, changing endocrine function, chronic diseases, inflammation, insulin resistance and nutritional deficiencies. This review aims to explore this latter issue.

Nutrition and sarcopenia

The key feature of sarcopenia most relevant to any nutritional aetiology is that it occurs in the physically active. Several studies have documented a loss of muscle strength in endurance-trained elderly men[5,6] who remained fit in terms of high aerobic power[5]. Similarly in sprint-trained athletes there is a clear loss of muscle function involving a decline in the maximum rate of force development which, in absolute terms at the age of 70 years, is greater than observed in a comparable untrained group, even though power output remains much higher[7]. The importance of these observations is that because physical activity increases energy expenditure and associated food intake, the physically active are highly unlikely to be undernourished. This means that sarcopenia is not a simple nutritional problem. The important question therefore is the extent to which nutrition can influence its development. One approach to reviewing what is known about nutrition and sarcopenia is to use and extend the framework of causality established by Little and Phillips.[8] They identified three main risk factors, inactivity, anabolic resistance and inflammation, and to these acidosis and vitamin D deficiency are added here (Fig. 1).

Inactivity: energy intakes

As it has been known for many years that strength training is quite effective in restoring the age-related losses in muscle mass and function[8–10] it is generally assumed that the main determinant of sarcopenia appears to be the decline in resistance-type physical activities[8,11–15]. While the atrophy of disuse, such as occurs with protracted bed rest is well described[8,10,16] it is less clear cut as to the extent to which variation in levels of physical activity within the normal population influences sarcopenia, mainly because of the difficulty of measurement. Low physical activity at work has been identified as a risk factor for sarcopenia[17] and a recent study indicated that muscle mass and strength in the elderly does respond to aerobic exercise[18]. This tends to suggest that sarcopenia is related to and might be minimised or even to some extent reversed by all types of muscle activity. What is not known is whether for adults in overall energy balance maintaining weight at varying habitual levels of physical activity, the varying levels of food energy intake influence sarcopenia independently from the varying levels of physical activity. Although excess energy intake that mediates weight gain, i.e. resulting in overweight or obesity, appears to usually result in increases in the fat-free mass (FFM), some of which can be assumed to be skeletal muscle, this is not always the case as indicated by the phenomenon of sarcopenic obesity. This is muscle loss in subjects becoming obese, and such a phenomenon makes it extremely difficult to draw any conclusion about whether low levels of food intake associated with inactivity are an independent risk factor for sarcopenia or whether high levels of food intake or excess energy intakes are protective. It might be expected that the effectiveness of strength training for reversing sarcopenia would require sufficient extra food energy to balance the energy cost of the increased physical activity, but in frail nursing-home elderly, the increase in strength with 10 weeks extremity resistance training was only slightly and non-significantly greater when the training was combined with an energy supplement[19] compared with training alone, even though overall energy intakes were markedly increased by the supplement. Similarly, while a high-intensity functional exercise programme has positive long-term effects in balance, gait ability and lower-limb strength for older persons, an intake of protein-enriched energy supplement immediately after the exercises did not appear to increase the effects of the training[20].

Anabolic resistance: dietary protein intakes

Several groups have identified anabolic resistance in human muscle[21–25] and Rennie's group have reported a blunting of both the stimulation of protein synthesis by amino acids[23] and the inhibition of proteolysis by insulin[25] in the healthy elderly compared with younger adults. This is linked to anabolic signalling deficits which mean that the nutrient signal provided by essential amino acids is not sensed or transduced as well by old muscle as it is by young muscle, resulting in a lower response of protein synthesis to the same nutrient stimulus. The actual location of these signalling deficits in muscle remain poorly understood[26]. The identification of anabolic resistance has obviously raised the question of whether increased protein intakes are required by the elderly to counteract it, which implies that sarcopenia is a result of inadequate dietary protein intakes.

Whether protein requirements for the elderly are increased because of anabolic resistance is not a straightforward question because there is a debate about the definition of protein requirement. Thus some argue that the conventional definition of the minimum intake to maintain
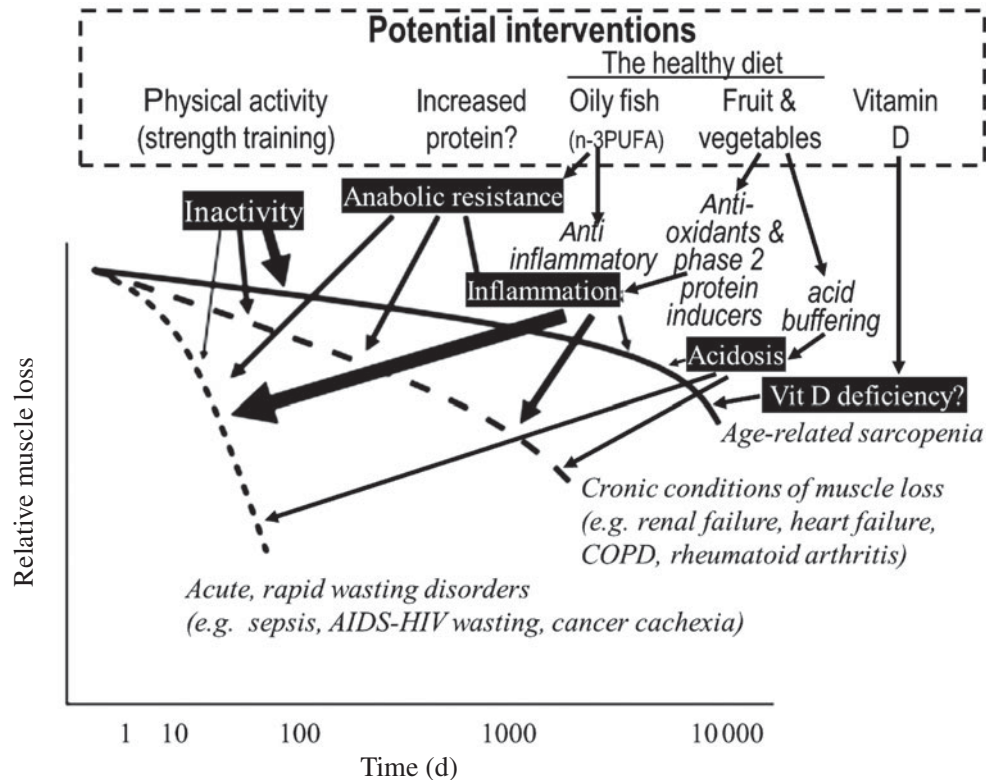
Fig. 1. Potential nutritional interventions in relation to putative physiological aetiological factors influencing sarcopenia (modified from[8]). COPD, chronic obstructive pulmonary disease.

the FFM as indicated by N balance is outdated and should be replaced by an optimal intake definition more related to health outcomes, with such a definition indicating the need by the elderly for higher protein intakes[27,28]. However, as reviewed by WHO[29] there is currently insufficient evidence to identify an optimal protein intake for the elderly or any population group. Certainly there is no convincing evidence for any change with age in balance estimates of the requirement. Our review of the early N balance evidence[30] indicated no change with age, which was also the finding of the meta analysis of N balance studies used by WHO/FAO in their report[29], and is supported by the most recent N balance study[31,32]. Experimental $^{13}C_1$ leucine balance studies also indicate no change in the efficiency of postprandial protein utilisation and a slight fall in the metabolic demand so that if anything there appears to be a slight fall with age[33,34]. So on this basis anabolic resistance does not appear to be influencing protein requirements, although given the very slow development of sarcopenia, it is unlikely that any balanced approach would be sensitive enough to identify anabolic resistance.

The recent Protein Report[29] did raise an important issue that needs to be taken into account. This involves the protein:energy ratio of requirements that does increase with age. The expression of protein (P) requirements as a ratio with energy (E) requirements, the P:E$_{requirement}$[29,35] is a useful term in relation to the identification of population groups most likely to be vulnerable to inadequate protein intakes when intakes are described by their protein density in terms of percentile protein energy. The mean

P:E$_{requirement}$ increases from quite low values in childhood (3·5–5 % P:E) to close to 10 % P:E in sedentary elderly women because energy requirements fall to a greater extent than protein requirements from childhood to old age. Thus older adults are the group most vulnerable to low-protein diets and need the most protein-dense food.

A second question then is, do the diets of elderly population groups provide enough protein to meet these requirements? My analysis of the UK National Diet and Nutrition Survey of protein intakes of the elderly[36] is shown in Figure 2. After trimming for under-reporting (removing energy intakes <1·35 × BMR median intakes were 1·24 g/kg per d, or 13·7 % food energy with no change with age within the elderly cohort and with an intake range of 0·5–2·38 g/kg per d. On the basis that prevalence of deficiency approximates to the proportion of the distribution with intakes below the average requirement[29,35] this indicates a negligible prevalence of deficiency. Furthermore the most recent National Diet and Nutrition Survey rolling programme[37] indicates that the average UK population consumes a diet containing higher protein intakes than previous surveys (17 % food energy), so that there should be no cause for concern at least for the healthy elderly population.

If sarcopenia resulted from inadequate protein intakes, this would mean that anabolic resistance could be overcome by higher protein intakes. In fact most studies indicate that protein intakes and sarcopenia are unrelated with only very limited evidence indicating a relationship. Most cross-sectional studies of sarcopenia and protein
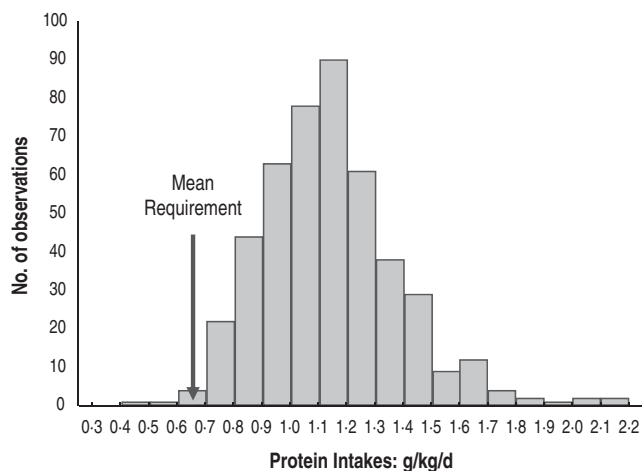
Fig. 2. Distribution of protein intakes in the UK elderly UK National Diet and Nutrition Survey trimmed for under reporters, (see text).

intakes published to date have failed to show any association[17,38–41]. One exception is a study reporting an association of dietary animal-protein intake with a muscle-mass index[42]. This involved a small cohort of older, mainly overweight women with a BMI up to 30, consuming a protein-rich diet. What was measured, described as the muscle-mass index, was FFM/height^2. This is arguably a poor index of sarcopenia in such a cohort because in the study FFM increased with BMI. Thus FFM/height^2 was highly correlated with BMI (r 0·714) and animal protein intake was correlated with BMI as well as FFM/height^2. What the results suggest to me is that the relationship between animal protein intake and FFM/height^2 is a consequence of meat and associated fat intake driving an increase in BMI and associated FFM rather than preventing a loss of muscle mass, which is how that data is discussed. Appendicular skeletal muscle mass was not directly measured in the study, so it is not possible to identify the extent to which sarcopenia *per se* occurred and how this was related to protein intake.

As for longitudinal studies of muscle mass and protein intake, few have been reported. An analysis of the 1993 and 1997 China Health and Nutrition Surveys of older adults (n 608, 50–70 years) reported that in those who lost muscle over the 4 years during surveys, muscle-mass change was not associated with protein intakes[43]. However, a recent large community-based 3-year longitudinal study of the loss of muscle from the arms and legs (appendicular lean mass (aLM)), (n 2066) in men and women aged[41] showed that the aLM loss was greater in the lowest compared with the highest quintile of protein intake. This was interpreted by the authors as suggesting that dietary protein may be a modifiable risk factor for sarcopenia in older adults and that higher intakes afford some protection. In fact some caution is needed in the interpretation of this study. Firstly as already indicated there was no relationship between aLM and protein intake at baseline when the dietary data were collected as others have found in cross-sectional studies, although there was no comment about this finding in the authors discussion. Most importantly the protein intake–△aLM relationship

during the 3-year longitudinal phase of the study was only observed for those who either lost or gained weight. The loss of aLM in the otherwise weight-stable subjects, half of the entire cohort, was not related to protein intake. This means that the relationship observed for the whole cohort is not a simple consequence of higher dietary protein intakes reducing sarcopenia and the author's conclusions of dietary protein being a modifiable risk factor for sarcopenia in older adults is not robustly supported by the data.

While the epidemiological evidence does not support an unequivocal relationship between sarcopenia *per se* and dietary protein intake, it is the case that epidemiological studies of protein intake in relation to health and disease are problematic because protein intakes do not vary as widely within most populations as fat and carbohydrate intake. Also measurement errors especially of intakes tend to attenuate associations between disease and diet. A recent very large prospective cohort study of older women, assessing protein intake in relation to frailty, attempted to correct intake measurement errors due to under reporting by adjusting protein intakes from an FFQ on the basis of a calibration algorithm derived from direct measures of energy expenditure by doubly labelled water studies and protein intakes indicated by 24 h urinary N excretion in a subset of the population[44]. Protein intakes were assessed at baseline and frailty was assessed after a 3-year follow-up by self-reported questionnaires of physical function, endurance or exhaustion, physical activity and unintentional weight loss. There was a reduced risk of frailty (adjusted for multiple variables) as the unadjusted or adjusted protein intakes (expressed as a % of energy intakes) increased. However, while it is likely that sarcopenia would contribute to frailty as measured, it is not possible to evaluate just how large this contribution was compared with the other indicators of frailty. The authors of this study take a cautious approach to interpreting the data discussing the potential of residual confounding, because of a strong relationship of protein intake and socio-economic status. Although the reported associations were adjusted for socio-economic status, residual confounding can never be ruled out leaving the possibility that protein intake served as a marker of better overall quality of life or diet quality.

Consistent with this lack of evidence of a relationship between sarcopenia and protein intakes, most intervention studies show that provision of dietary supplements to elderly subjects are ineffective in improving lean body mass (LBM)[19,45–47]. Two recent reviews of protein intake in relation to resistance exercise have concluded that no synergistic effect of protein supplementation and resistance exercise has been identified in aging populations[47,48] and a subsequent report showed that modestly increasing protein intake (from 0·9 to 1·2 g/kg per d), predominantly from eggs, had no influence on the gain in muscle induced by resistance training in older people[49]. Also a recent task force on sarcopenia[50] concluded 'it is not clear if protein supplementation in the absence of malnutrition enhances muscle mass and muscle strength, as protein supplementation alone or in association with physical training has proved unsuccessful'. I am aware of only three intervention studies with amino acid supplements which have

shown positive influences. An uncontrolled 3-month amino acid supplementation at 12 g/d improved walking function and grip strength in more sedentary and frail elderly[51]. Another small uncontrolled 16-week trial of dietary supplementation with an essential amino acid mixture plus arginine in glucose intolerant elderly subjects[52] found improvements of LBM, muscle strength and physical function. The third was an 18-month study of 8 g/d of an essential amino acid supplement given to elderly subjects with reduced LBM and sarcopenia[53]. Significant increases in leg, arm and trunk lean mass measured by dual energy X-ray absortiometry were reported after 6 months and more consistently after 18 months. Although this latter study is described as a randomised, placebo-controlled crossover study, in which two 4-month supplement/placebo intervention periods were followed by a further 8-month period in which both groups were supplemented, the gains in LBM are only shown after 8 and 16 months. The changes in LBM for the supplement and placebo at the end of each crossover period were not shown, which negated the placebo-control nature of the design. Nevertheless the interventions did restore some of the depleted muscle mass and since it was an open-label study this would reduce the possibility of a placebo effect.

Clearly these latter studies are intriguing given the general background of a lack of evidence connecting dietary protein to sarcopenia and certainly provide sufficient evidence to warrant further randomised controlled trials (RCT).

Inflammation: protection by the healthy diet

Inflammation is now known to be an important part of the mechanism of many diseases[54,55] and as suggested by Little and Philips[8], while inflammation is certainly part of the mechanism leading to severe muscle wasting in several disease states there is evidence of its involvement in the aetiology of sarcopenia. As indicated above abdominal adiposity and sarcopenia can be linked through inflammation deriving from adipocytes[3,4]. Reactive oxygen species and other inflammatory mediators can act through NF-κB to induce pro-inflammatory cytokines[55] and reactive oxygen species produced during oxidative stress can directly mediate muscle damage. When this occurs with aging there is a decline in cellular and tissue function and damaged proteins give rise to the accumulation of protein carbonyls which is a measurable indication of oxidative damage[56]. The importance of this was shown in a cross-sectional study of women living in the community aged ≥ 65 years, from the Women's Health and Aging Study[57]. Serum protein carbonyl concentrations were a powerful independent predictor of low grip strength. As several dietary components protect against inflammation, a lack of adherence to the principles of the healthy diet could be an important dietary influence on the development of sarcopenia.

One such component is oily fish through their provision of very long-chain n-3 PUFA[54,58,59] and some very recent evidence suggests that this may well be important. Thus an 8-week supplementation of older adults with 4 g EPA +

DHA or corn oil attenuated the anabolic resistance in older adults by augmenting the amino acid–insulin-induced increase in muscle protein synthesis by increasing activation of the mammalian target of rapamycin–70-kDa ribosomal protein S6 kinase signalling pathway[60]. However, they found no effects on serum markers of inflammation possibly because they specifically selected healthy persons with low plasma concentrations of inflammatory markers for their study. So the mechanism of action of this intriguing finding is not clear, but it certainly warrants long-term trials to investigate any effect on muscle strength or mass.

The healthy diet includes abundant fruit and vegetables, which provide both antioxidants and inducers of phase 2 proteins which are mainly enzymes that inactivate electrophiles and strong oxidants. Semba et al.[61] reviewed evidence that carotenoids protect against sarcopenia in older adults identifying four studies showing low serum carotenoids to be independently associated with sarcopenia. The concentration of plasma vitamin C in community-dwelling elderly Japanese women has been shown to be a significant determinant of muscle strength and physical performance[62]. One dietary source of phase 2 protein inducers is cruciferous vegetables with broccoli sprouts containing glucoraphanin, which is metabolised into the phase 2 protein-inducer sulforaphane[63]. Administration of this in rats significantly decreased oxidative stress in several tissues as shown by an increase in the reduced form of glutathione, glutathione reductase and glutathione peroxidase activities and decreased protein nitrosylation[63]. In mice, administration of a synthetic phase 2 protein inducer 2(3)-tert-butyl-4-hydroxyanisole resulted in healthier aging in terms of an antioxidant response activation, decreased oxidative stress and decreased pro-inflammatory gene expression, with less weight gain and better locomotor function[64]. Finally, the anabolic resistance of muscle protein synthesis to stimulation by increasing leucine concentrations observed in older rats was reversed by a 7-week dietary treatment with an antioxidant mixture containing rutin, vitamin E, vitamin A, Zn and Se[65].

Acidosis: protection by the healthy diet

Another important benefit of fruit and vegetables is their provision of K salts of weak organic acids which can buffer acid, mainly sulphuric and phosphoric acid deriving from the catabolism of the S amino acids and phytates. It has long been known that acidosis has marked catabolic influences on muscle[66] and in postmenopausal women the administration of K bicarbonate reduces urinary N excretion[67] by an amount (0·4 kg LBM in 18 d) which is potentially sufficient to both prevent continuing age-related loss of muscle mass and restore previously accrued deficits. The fact that exogenous base did reduce blood acidity and increased plasma bicarbonate concentration, indicates that a normal diet can result in a low-grade metabolic acidosis so that diets with increased fruit and vegetables and a lower potential renal acid load should have a similar influence. This has been reported. Older subjects studied in a 3-year trial of Ca and vitamin D showed that 24-h

urinary K was significantly positively associated with %LBM at baseline[68]. Furthermore, the magnitude of the relationship indicated a protective effect of the highest K intake similar to that reported by Frassetto et al.[67]. The authors suggest that some of the loss of lean tissue mass that occurs with aging can be prevented by increasing the intake of foods rich in K, such as fruit and vegetables, to the recommended level.

Vitamin D: strength preservation in muscle

There is intense interest currently in vitamin D with a recent US Institute of Medicine (IOM) report on Dietary Reference Intakes which provides a comprehensive review of published work on vitamin D up to 2010[69]. The report identifies vitamin D as necessary for normal development and growth of muscle fibres, with its deficiency adversely influencing muscle strength and contributing to poor physical performance, and with muscle weakness and pain (myopathy) characteristics of severe deficiency (rickets and osteomalacia). In their review of potential indicators of adequacy and selection of indicators from which to derive recommended intakes they argue that vitamin D-deficiency related muscle weakness and the implications of poor muscle tone suggest a relationship between serum 25-hydroxy vitamin D (25(OH)D) and risk of falling and/or poor physical performance in susceptible populations. Sarcopenia was not specifically examined in the report but the idea that vitamin D deficiency is a contributing factor is plausible. Certainly the muscle changes in adults with severe vitamin D deficiency, predominantly type II muscle fibre atrophy[70], are similar to the changes observed in sarcopenia[1,8]. Also at least one report identifies vitamin D deficiency as a risk factor for sarcopenia. Thus in a prospective study of 845 Frenchmen aged 45–85 years, those with serum 25(OH)D <10 ng/ml, (25 nmol/l), had significantly lower appendicular muscle mass than those with 25(OH)D ≥ 30 ng/ml (75 nmol/l). However, these vitamin D deficient men represented only thirty-three out of 845 men[17] and for the remaining 812, 25(OH)D did not predict muscle mass.

The IOM committee examined evidence published up to 2010 on falls and physical performance and overall found a lack of sufficiently strong evidence to support Dietary Reference Intake development. It is the case that their approach to causality was cautious with most reliance given to RCT and this has been criticised[71–73]. Thus while they identified some support for an association between serum 25(OH)D levels and physical performance they noted that high-quality observational evidence from large cohort studies was lacking. Also, while they found that data from RCT suggests that vitamin D dosages of at least 20 μg (800 IU)/d may confer benefits for physical performance measures, and that high doses of vitamin D (i.e. ≥ 20 μg (800 IU)/d) provide greater benefit for physical performance than low doses (i.e. 10 μg (400 IU)/d), they argued that the evidence is insufficient to define the shape of the dose–response curve for higher levels of intake. It is the case that 25(OH)D was shown to predict lower-extremity function in both active and inactive persons aged ≥ 60 years[74] and a meta analysis of RCT of vitamin D supplementation showed a >20 % reduced risk of falls among ambulatory or institutionalised elders[75]. Furthermore, the more recent suggestion in a systematic review that the association between vitamin D and physical performance remains controversial[76] appeared to be resolved by an updated meta analysis of RCT in which studies were separated according to intervention dose[77]. This showed that supplemental vitamin D reduced the risk of falling among older individuals by 19 % for interventions ≥ 17·5 μg (700 IU)/d but not at lower doses and that serum 25(OH)D <60 nmol/l may not reduce the risk of falling. However, the IOM committee argues that this meta analysis as conducted has major limitations in its methodology in relation to both the inclusion and exclusion of studies and in the actual meta-regression analysis. Their reanalysis indicated a non-significant dose–response relationship between the risk of sustaining at least one fall and the daily dose of vitamin D supplementation or achieved serum 25(OH)D. Furthermore, they identified two recent (2010) intervention studies that failed to show efficacy in reducing falls[78,79]. Overall, of the eighteen studies they considered, only four found a significant effect of vitamin D on fall incidence. Their overall conclusion in terms of a causal relationship between vitamin D intakes or achieved blood level and incidence or risk for falls was that such a relationship was not supported by the evidence published to date.

In fact, notwithstanding enthusiastic reviews relating vitamin D status to muscle strength and function[80,81], in addition to the cautious approach of the IOM report in relation to vitamin D status and muscle function there are two other important issues that need to be resolved.

Firstly, there is some controversy about whether skeletal muscle is an important direct target of vitamin D action, which is generally accepted to be the case by the IOM committee and most reviewers[80]. The biologically active form of vitamin D, 1,25-dihydroxyvitamin D, is believed to act through the vitamin D nuclear receptor (VDR), modulating the expression of genes related to the regulation of Ca transport, cell proliferation and differentiation and other actions, and a less clearly defined cell membrane receptor, which mediates some rapid non-genomic actions of 1,25-dihydroxyvitamin D. A sizeable proportion of the human genome contains vitamin D response elements[69,82] with the VDR widespread throughout the body including, according to most observers, the muscle. For example Ceglia et al.[83] have recently shown nuclear VDR associated with most myonuclei from all muscle fibre types observed in a human muscle biopsy, as well as in peripheral areas of the muscle fibre not connected with a myonucleus, possibly indicating the putative membrane-associated VDR believed to activate rapid, non-genomic, second messenger intracellular signalling cascades[80]. However, De Luca's group have challenged the existence of VDR in muscle, failing to identify them in their own studies[84]. They report that their specific and sensitive immunohistochemical assay with antibodies that do not detect proteins in tissues from VDR null mice but does identify VDR in rat duodenal tissue, does not detect the VDR in skeletal, cardiac or smooth muscle, including

human cardiac and skeletal muscle. They argue that previous studies of *in situ* immunohistochemical detection of VDR in human skeletal muscle tissues (e.g.[85]) involve antibodies that react with proteins on Western blot not related to VDR and detect proteins in extracts prepared from VDR null mice that have no VDR. This report follows another recent study from this group showing that in the rat, the muscle weakness of severe vitamin D deficiency is an indirect effect, mediated through hypophosphatemia induced by the traditional role of vitamin D in regulating plasma PO_4 (and Ca) levels[86]. Ceglia *et al.*[83] make no comment about the likelihood of cross reactivity of their primary mouse, anti-human VDR monoclonal antibody that does differ from those used in previous studies. Clearly this is an issue that requires resolution because vitamin D action on muscle might be expected to be potentially much more subtle and wide-ranging if mediated through multiple genomic and non-genomic receptor-mediated mechanisms than through a single indirect mechanism relating to PO_4 availability.

Secondly, if vitamin D status did prove to be a significant risk factor for sarcopenia, the extent to which it is equally important in men and women has been questioned. According to Ceglia *et al.*[87], an association between serum 25(OH)D and muscle-related outcomes in published studies appears to be strongest in older female-only populations. They report a recent cross-sectional study of serum 25(OH)D and physical function in adult men, which indicates no association between serum 25(OH)D and LBM, muscle strength and physical function after controlling for age, racial and/or ethnic group and multiple lifestyle factors. They cite several studies in which declining muscle function or mass varies with vitamin D status in women but not men, and a previous RCT with 25 μg (1000 IU) vitamin D in elderly men which did not increase muscle strength or improve physical performance over a 6-month period[88]. It is the case that the cohort examined in this recent study included both young and older men who were not recruited with evidence of physical impairment and vitamin D insufficiency. Thus although the majority of the men had serum 25(OH)D <75 nmol/l, a commonly accepted target level, only 19% had 25(OH)D <50 nmol/l, the cut-off for adequacy identified by the IOM report[69]. As indicated above in the study[17] in which vitamin D deficiency was identified as a risk factor for sarcopenia, only those with very low 25(OH)D levels (<25 nmol/l) had reduced muscle mass. It may be therefore that while severe vitamin D deficiency is a risk factor for sarcopenia in men and women, variation in 25(OH)D >25 nmol/l is only likely to influence muscle function in women. Clearly there is an urgent need for more work in this area.

Conclusions and key messages

In this review while the focus has been on nutrition and sarcopenia *per se* (age-related loss of skeletal muscle), because of the limited amount of specific information, the evidence reviewed has also included studies examining potential aetiological factors, as well as nutritional aspects of functional decline relating to sarcopenia such as

dynapenia and in one case frailty. Because of this the conclusions reached must be recognised as tentative. As already argued, the occurrence of sarcopenia and dynapenia in population groups who remain physically active indicates that a simple nutritional aetiology is unlikely, and this should limit expectations of what is likely to be achievable through dietary interventions. Nevertheless in the context of the most widely discussed mechanisms of sarcopenia shown in Fig. 1 it would appear that there is sufficient evidence to expect sarcopenia, like many other age-related morbidity to be minimised by a healthy lifestyle and a healthy diet: for example, maintain as much physical activity and energy expenditure as possible to ensure an appropriate appetite for sufficient food intake to ensure a healthy balanced diet that maintains a healthy body-weight, minimizing inflammation associated with excess adiposity. For populations with limited mobility, who are frail and for whom consumption of sufficient of the healthy diet to ensure nutritional adequacy for all macro and micronutrients is difficult, the evidence base for the effectiveness of specific supplements is currently fragmentary but sufficient to warrant further studies with supplements of essential amino acids, antioxidants and phase 2 protein inducers, fish oil and vitamin D. However, for the mobile active elderly, a healthy diet in which the potential renal acid load of protein-rich foods is balanced by base from a rich supply of fruit and vegetables, which will also minimize any inflammatory damage, and with frequent oily fish to ensure intakes of both *n*-3 long-chain PUFA and vitamin D, with the latter boosted by summer sunshine, is clearly the appropriate advice for the enjoyment of a healthy independent old age.

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