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The role of dietary protein and vitamin D in maintaining musculoskeletal health in postmenopausal women: A consensus statement from the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO)

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ABSTRACT

From 50 years of age, postmenopausal women are at an increased risk of developing sarcopenia and osteoporosis as a result of deterioration of musculoskeletal health. Both disorders increase the risk of falls and fractures. The risk of developing sarcopenia and osteoporosis may be attenuated through healthy lifestyle changes, which include adequate dietary protein, calcium and vitamin D intakes, and regular physical activity/exercise, besides hormone replacement therapy when appropriate. Protein intake and physical activity are the main anabolic stimuli for muscle protein synthesis. Exercise training leads to increased muscle mass and strength, and the combination of optimal protein intake and exercise produces a greater degree of muscle protein accretion than either intervention alone. Similarly, adequate dietary protein intake and resistance exercise are important contributors to the maintenance of bone strength. Vitamin D helps to maintain muscle mass and strength as well as bone health. These findings suggest that healthy lifestyle measures in women aged >50 years are essential to allow healthy ageing. The European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO) recommends optimal dietary protein intake of 1.0–1.2 g/kg body weight/d with at least 20–25 g of high-quality protein at each main meal, with adequate vitamin D intake at 800 IU/d to maintain serum 25-hydroxyvitamin D levels >50 nmol/L as well as calcium intake of 1000 mg/d, alongside regular physical activity/exercise 3–5 times/week combined with protein intake in close proximity to exercise, in postmenopausal women for prevention of age-related deterioration of musculoskeletal health.

Abbreviations: 25(OH)D, 25-hydroxyvitamin D; BMD, bone mineral density; DXA, dual-energy X-ray absorptiometry; HRT, hormone replacement therapy; IGF-I, insulin-like growth factor-I; mTOR, mammalian target of rapamycin; QoL, quality of life; RCT, randomized controlled trial; RNI, recommended nutrient intake; VDR, vitamin D receptor.

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1. Introduction

Age-related alterations in musculoskeletal health include a decline in muscle mass and strength, known as sarcopenia [1], and reductions in bone mineral density (BMD) and bone strength, known as osteoporosis [2]. Both phenomena are responsible for a higher risk of falls and fractures, and resulting disability, loss of independence, decreased quality of life (QoL) and increased mortality [3,4]. The loss of muscle mass and strength with ageing is associated with multiple factors including reduced dietary protein intake, resistance of muscle protein synthesis to anabolic stimuli, low vitamin D intake, reduced physical activity, and the menopause in women [5,6]. Sarcopenia is now recognized as a major clinical problem in the older population. Estimates of the prevalence of sarcopenia in older people worldwide have varied from 3% to 30% according to the operational definition implemented [7]. Recent convergence of the operational definition of sarcopenia combines measures of muscle mass and strength or physical performance [3,8–10]. Accordingly, the prevalence of sarcopenia in community-dwelling older people in the UK was found to be between 5% and 8% in men and women (mean age 73 and 67 years) [7], which is consistent with other population-based studies that found the prevalence of sarcopenia in those aged >60 years to be 7–12% [11–13]. A significantly higher prevalence of sarcopenia approaching 30% was found among those aged >80 years [11,12]. Men and women with sarcopenia were found to be shorter than those without, weighed less, and had worse physical performance and poorer self-reported general health and physical functioning scores [7]. The socioeconomic relevance of sarcopenia has been demonstrated by direct healthcare costs caused by this syndrome, which were estimated at $18.5 billion for the USA in 2000 [14]. Strikingly, a decrease in the prevalence of sarcopenia by only 10% would save $1.1 billion per year in US healthcare expenditures.

Osteoporosis, another age-related disease, is associated with low BMD, microarchitectural disruption of the bone, bone tissue fragility and an increased risk of fractures [15]. Osteoporosis is more common in women, affecting over 22 million women aged >50 years in Europe, or 22% of the female population in 2010 [4]. At the age of 50 years, the lifetime probability of a hip fracture is 7–25%, and is close to 50% for major osteoporotic fractures among European women. In 2010, 3.5 million new fragility fractures were sustained. The resulting total direct cost of osteoporosis in 2010 was estimated at €37 billion, posing a large burden on healthcare resources [4].

Between 2000 and 2050, the proportion of the world's population aged >60 years is predicted to double from 11% to 22%. The absolute number of people aged ≥60 years is expected to increase from 605 million to 2 billion by 2050, and the number of people aged ≥80 years will quadruple to 395 million by 2050 [16]. Many of the very old lose their ability to live independently because of limited mobility and frailty. With increasing age, it is important to maintain health and independence, which in turn keeps the necessary level of care low and QoL high. Osteoporotic fracture risk increases sharply during the seventh decade of life, and the prevalence of sarcopenia rises sharply with increasing age, which contributes to the fracture risk, thus preventive therapy beforehand is important in those likely to be at increased risk of future fracture.

Osteoporosis and sarcopenia share many of the same risk factors and both directly or indirectly cause an increased risk of mobility limitations, falls, fractures and disability. This is not surprising since bones adapt their morphology and strength to the long-term loads exerted by muscle during anti-gravitational and physical activities. Non-mechanical systemic and local factors also modulate the mechanostat's effect of muscle on bone by affecting the bidirectional osteocyte–muscle crosstalk, but the specific mechanisms that regulate these homeostatic mechanisms are not fully understood [17]. A better understanding of the muscle–bone physiological interaction and of lifestyle factors that influence sarcopenia and osteoporosis may help in the development of preventive strategies that reduce the burden of musculoskeletal diseases and consequent disability in older persons and limit the financial burden associated with such conditions.

Fig. 1. Age-related alteration in musculoskeletal health.
Source: Barry et al. J Gerontol A: Biol Sci Med Sci; 2004 [1].

Existing evidence indicates the potential importance of diets of adequate quality, to ensure sufficient intakes of protein, calcium and vitamin D, and regular physical activity [18,19]. At every stage of life, adequate dietary intakes of key bone nutrients including calcium, vitamin D and protein contribute to muscle and bone health, thereby reducing the risk of falls, osteoporosis and fractures in later life [20]. Recent guidelines have focused on steps to reduce risk in elderly populations [21–23]; however, no clear consensus has been given to guide healthy nutrition and lifestyle among postmenopausal women to optimize musculoskeletal health in later life. The Task Force of the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO) has sought to provide consensus recommendations for optimal daily intake of dietary protein and vitamin D, and physical activity and exercise.

2. Loss of muscle mass and strength with ageing

Sarcopenia is a syndrome characterized by progressive and generalized loss of skeletal muscle mass and strength, with a risk of adverse outcomes such as physical disability, poor QoL and death [3]. Muscle mass and to a greater extent muscle strength and power decline with age (Fig. 1) [1], and age-associated changes in muscle strength lead to a deterioration of functionality. A steep decline in muscle mass has been detected in men and less prominently in women, while a significant increase in fat mass is noted for both sexes [24–26]. Age-related alterations in skeletal muscle [27] include changes of fat and collagen content as well as structural changes. After about age 50, muscle mass decreases at an annual rate of 1–2% [28]. Muscle strength declines by 1.5% between 50 years and 60 years and by 3% thereafter. The reasons for these changes include denervation of motor units and a net conversion of fast type II muscle fibres into slow type I fibres with resulting loss in muscle power necessary for activities of daily living. Once muscle mass in elderly people falls below 2 standard deviations of the mean of a young control cohort and the gait speed falls below 0.8 m/s, a clinical diagnosis of sarcopenia can be reached [28]. Studies have shown that the risk of falls is significantly elevated in individuals with reduced muscle strength [27].

A more accelerated loss of muscle mass and strength has been suggested to occur in various clinically compromised older populations, such as those who are obese, have type 2 diabetes mellitus, or cardiovascular disease, and has been referred to as a sort of accelerated ageing. For example, older patients with type

2 diabetes mellitus show an accelerated decline in leg lean mass, muscle strength, and functional capacity when compared with non-diabetic controls [29]. A decline in lean muscle mass over a 7-year period may be detected in an ageing population (70–85 years) even with high fitness levels [30]. In contrast, low fitness in old age was associated with greater weight loss and loss of lean mass than with high fitness. A correlation between muscle mass index and degree of disability has been demonstrated, with the results for older women (age >60 years) forming a U-shaped curve for skeletal muscle index (kg/m^2) versus degree of disability [31]. The incidence of physical disability was increased in women with both low and very high skeletal muscle index values. Women with low skeletal muscle mass had odds for physical disability of >3, while women with very high skeletal muscle index had physical disability risk that may, in part, reflect the increased fat mass and obesity in these women [31]. Leg muscle mass could be expected to correlate with muscle strength [32]; however, the age-related decline in muscle strength is greater than the loss of muscle mass [33]. In a meta-analysis, Manini has found a poor correlation between muscle mass and strength [34]. Loss in muscle strength is reflected by tests of functionality such as gait speed, which decreases with age, and that correlates with the risk of institutionalization and survival [35,36]. Thus, it appears that muscle strength is more important than muscle mass. Additionally, sarcopenia may be optimally defined using a combination of measures of muscle mass and physical performance [9]. Based on these observations strength and/or tests of functionality have been included in the recently proposed definitions of sarcopenia [3,8,10].

3. Impact of menopause on musculoskeletal health

The onset of the menopause is associated with a natural decline in oestrogen that increases visceral fat mass, and decreases BMD, muscle mass, and strength. The rapid decline in BMD after the menopause results in an increased risk of fractures in the classic sites of vertebrae, distal forearm and proximal femur [37]. The onset of menopause and loss of ovarian function is associated with a significant increase in the prevalence of osteoporosis, which continues to increase through the postmenopausal period [15]. Hormone replacement therapy (HRT) has been demonstrated to reverse the loss in BMD associated with the menopause [38] and reduce the risk of wrist, hip and spine fractures [39]. HRT can be recommended as effective and appropriate for the prevention of osteoporosis-related fractures in at-risk women before age 60 years or within 10 years of menopause [40–42]. However, initiating HRT after the age of 60 years for the sole purpose of the prevention of osteoporotic fractures is not recommended [41].

In women, an accelerated loss of muscle mass and strength occurs at an earlier age than in men, around the time of menopause [5]. Loss of muscle strength, and to a greater degree muscle power, is of a higher magnitude than the changes observed in muscle mass [1], showing the importance of muscle quality and neuromuscular function when considering sarcopenia. Muscle strength and/or power are correlated with oestrogen levels [43], and a significant decrease in muscle power is demonstrated in postmenopausal women [44]. Oestrogen receptors are present in human muscles located in the nuclei of muscle fibres and capillaries, and the number of oestrogen receptors found in muscle is higher among men, young women and children than in postmenopausal women [5]. Experimental studies indicate that skeletal muscle is an oestrogen-responsive tissue, with estradiol acting through oestrogen receptors in skeletal muscle to cause an improvement in the function of myosin and ultimately improvement in muscle strength [43]. Oestrogen replacement improves myosin function and strength in muscle that is devoid of sex hormones and the content of oestrogen receptors in muscle also increases. HRT appears to be associated with greater muscle power, regulation of muscle contraction, and favourable muscle composition among younger postmenopausal women (50–65 years) [45,46]. Whether HRT is a preventive agent for muscle weakness and mobility limitation in older postmenopausal women requires further long-term studies. HRT in combination with resistance exercise may help to improve muscle strength in postmenopausal women [43].

Women with a tendency to postural instability may need power and high velocity strength to protect themselves from falls, which are associated with an increased fracture risk in postmenopausal women because of the decrease in BMD [5]. Thus, the bone loss and deterioration in muscle strength and power that occurs in women after the menopause can have a negative impact on physical function and QoL.

Section summary:

- Muscle mass and, to a greater extent, muscle strength and power decline with age, and age-associated changes in muscle strength lead to a deterioration of functionality.
- Sarcopenia is a syndrome characterized by progressive and generalized loss of skeletal muscle mass and strength with a risk of adverse outcomes such as physical disability, poor QoL and death.
- In women, the onset of the menopause is associated with a natural decline in oestrogen that increases visceral fat mass, and decreases BMD, muscle mass and strength, which can have a negative impact on physical function, increase the prevalence of osteoporosis, and increase fracture risk.
- HRT is demonstrated to reverse the loss in BMD after the menopause, and is associated with greater muscle power, regulation of muscle contraction, and favourable muscle composition among young postmenopausal women (50–65 years).

4. Regulation of muscle synthesis

Any loss of muscle protein results from an imbalance between muscle protein synthesis and muscle protein breakdown, although the cause of the imbalance in age-related sarcopenia is incompletely defined. Lean tissue mass and function depend on continuous rebuilding of proteins. It has been reported that basal, fasting whole body and muscle protein synthesis rates are reduced in the older population [47]; mixed muscle protein synthesis declines with age at a rate of 3.5% per decade from age 20 years to 90 years [47]. However, differences in basal muscle protein turnover between old and young men do not appear to explain the muscle loss that occurs with age [48]. Therefore, more recent research has focused on the muscle protein synthetic response to the main anabolic stimuli (i.e. food intake and physical activity in the older population) [32]. Splanchnic protein metabolism is modified by age, but this metabolic change is not associated with a lower synthesis rate of muscle protein, provided that high plasma levels of essential amino acids are maintained [49].

Exercise can enhance muscle protein synthesis irrespective of age. In one study, exercise training increased mixed muscle protein synthesis by 22% with no effect of age on the response [47]. The ingestion of protein and amino acids stimulates muscle protein synthesis [50]. A marked increase in whole-body protein synthesis is observed upon feeding and is partly attributed to an increase in muscle protein accretion. However, the anabolic sensitivity of skeletal muscle tissue to protein feeding seems to become reduced with ageing [51], and has led to the concept of anabolic

resistance occurring with advanced age [52]. Anabolic resistance may be affected by a number of factors including dietary protein digestion rate, amino acid absorption, plasma amino acid availability, hormonal response, postprandial perfusion, and myofibrillar protein synthesis [52].

The impact of postprandial protein digestion on muscle synthesis has been studied. The more amino acids become available following meal ingestion, the greater postprandial muscle protein synthesis rates are generally observed. Besides protein digestion and absorption kinetics, different protein sources may vary in their capacity to stimulate postprandial muscle protein synthesis rate [53]. This is likely to be attributed to differences in amino acid composition, with different amino acids eliciting different anabolic responses. Whey protein ingestion stimulates postprandial muscle protein accretion more effectively than the ingestion of intact or hydrolysed casein in older men [54]. This effect probably results from both the more rapid digestion and absorption of whey protein and also the higher leucine content of whey compared with casein [54]. Leucine is a key anabolic amino acid that exerts a dose response effect on muscle protein synthesis [53]. Leucine co-ingestion with a bolus of dietary protein can further augment postprandial muscle protein synthesis rates in elderly men [55,56]. Elderly people have a decreased ability to respond to anabolic stimuli such as insulin and amino acids compared with young people. Following the administration of mixed meals the stimulation of muscle protein synthesis is reduced in elderly people, due to insulin resistance, and the anabolic effect of amino acids appears blunted at low doses. Recent studies have highlighted that these age-related alterations in amino acid metabolism may be overcome by the provision of excess leucine, changes in the daily protein intake pattern, or increased exercise, which improve muscle protein synthesis [57].

Section summary:

- Food intake and physical activity are key anabolic stimuli for muscle protein synthesis. Exercise can enhance muscle protein synthesis irrespective of age.
- The ingestion of protein and amino acids stimulates muscle protein synthesis; however, the anabolic sensitivity of skeletal muscle tissue to protein intake is reduced with ageing, leading to the concept of anabolic resistance.
- Different protein sources may vary in their capacity to stimulate the rate of postprandial muscle protein synthesis. Leucine is a key anabolic amino acid that exerts a dose response effect on muscle protein synthesis, and is demonstrated to increase rates of postprandial muscle protein synthesis in elderly men.

5. Dynamic relationship between protein, muscle and bone health

Mechanisms for alterations of protein use in older persons are threefold: inadequate intake of protein (anorexia of ageing), reduced ability to use available protein (e.g. anabolic resistance, tissue redistribution of amino acids), and a greater need for protein (inflammatory diseases) (Fig. 2) [21]. There is evidence that dietary proteins have a direct effect on key regulatory proteins and growth factors involved in muscle and bone growth, such as mammalian target of rapamycin (mTOR) and insulin-like growth factor-I (IGF-I). Branched-chain amino acids lead to activation of mTOR and aromatic amino acids (which are particularly prevalent in dairy protein) lead to increased IGF-I resulting in greater muscle mass and strength [58,59] (Fig. 3). Guidelines for dietary protein intake advise similar intake for all adults, regardless of age, at around 0.8 g

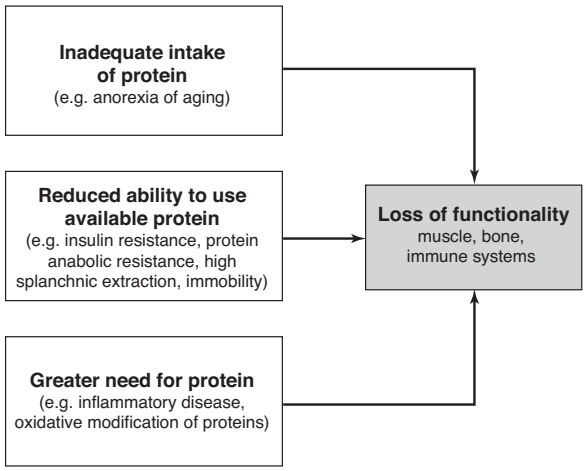

Fig. 2. Age-related causes of protein shortfall, leading to impairment of muscle, skeletal and immune function.
Source: Bauer et al. JAMDA; 2013 [21].

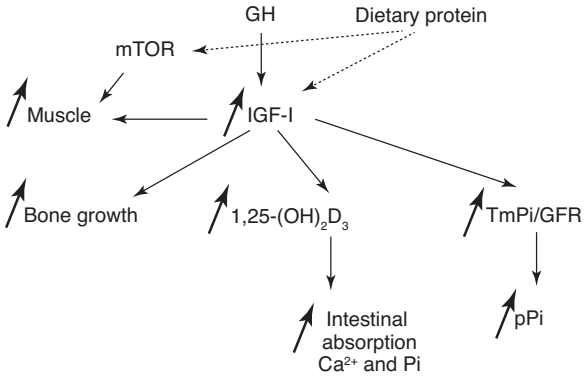

Fig. 3. Pathways through which dietary protein influences muscle anabolism and bone growth. A dietary protein-mediated increase in the circulating level of IGF-I enhances the renal production of 1,25-$(OH)_2D_3$, which stimulates the intestinal absorption of calcium and inorganic phosphate, and increases the tubular reabsorption of inorganic phosphate. This indirectly influences bone mineralization. Dietary protein influences muscle anabolism through amino acids and IGF-I mediated effects on muscle mass and strength. 1,25-$(OH)_2D_3$, 1,25-dihydroxyvitamin-D_3 (biologically active form); Ca++, calcium; GH, growth hormone; IGF-I, insulin-like growth factor-I; mTOR, mammalian target of rapamycin; Pi, inorganic phosphate; pPi, plasma inorganic phosphate; TmPi/GFR, maximum tubular reabsorption of Pi per unit volume of glomerular filtration rate.

of protein per kilogram of body weight each day (g/kg BW/d) (or 46–52 g/d) [60–62]. A low dietary intake of protein (0.45 g/kg BW) in elderly women is associated with a reduction in plasma IGF-I levels and skeletal muscle fibre atrophy [63]. Both high and moderate protein intake in the elderly are associated with reduced mortality, suggesting that protein intake representing at least 10% of the calories consumed may be necessary after age 65 years to prevent age-related weight loss and reduction in IGF-I and of other important factors [64]. Protein intake representing 17–21% of total daily calories is recommended among adults of all ages [65].

Data from the National Health and Nutrition Examination Survey (NHANES) 2003–2004 demonstrates that protein intake (g/kg BW/d) decreases with increasing age, with daily protein intake averaging 91 ± 22 g/d among adults aged 19–30 years, decreasing to approximately 66 ± 17 g/d in the elderly [65]. Among women included in the NHANES survey, 8% of adolescent females and 7–9% of older adult women reported consuming protein levels below their estimated average requirement [65]. Among the elderly, protein intake is found to be below the estimated average

daily requirement in 35% of institutionalized elderly people and in 10% of community-dwelling frail elderly people [66]. Institutionalized elderly people have especially low nutritional protein intake at breakfast [66]. The distribution of protein intake over the day may be important, and it is proposed that 20–25 g of dietary protein per meal is required to allow an appropriate stimulation of postprandial muscle protein synthesis over a 24-h period, which is more effective than skewing protein intake towards an evening meal [32,54,67,68]. However, other studies support the concept of protein pulse feeding (e.g. a main high protein meal, usually at midday) [69]. The results from muscle protein anabolism studies, along with appetite regulation and satiety research suggest that meeting a protein threshold at each meal (of approximately 30 g/meal) represents a promising strategy for middle-aged and older adults concerned with maintaining muscle mass while controlling body fat [70].

Dietary protein intake correlates with appendicular lean mass; in community-dwelling adults, participants in the highest quintile of protein intake lost 40% less lean mass than did those in the lowest quintile over 3 years [71]. The least muscle loss was seen in the elderly (aged 70–79 years) consuming protein at 1.1 g/kg/BW/d or 18% of total energy intake [71]. Further, increased protein intake in postmenopausal women is correlated with high lean body mass [72]; compared with those in the lowest tertile of protein intake (<66 g/d), women in the top tertile (>87 g/d) had 5–6% higher whole body and appendicular lean mass and 5–6% higher whole body and appendicular bone mineral content. High protein intake is also correlated with increased physical function [73]. While protein supplementation in frail elderly people has no impact on total lean mass, an improvement in muscle mass gain during exercise training in frail elderly people has been observed and an increase in functional ability demonstrated [74,75]. Protein energy supplementation is seen to reduce functional decline in frail older adults [76] and improve physical performance [74]. Elderly persons who have osteoporotic hip fracture are often undernourished, particularly with respect to protein, and protein malnutrition may contribute to the occurrence and outcome of hip fracture. In a study of elderly persons with recent osteoporotic hip fracture, protein supplementation was associated with increased serum IGF-I, attenuation of proximal femur bone loss, and shorter stay in rehabilitation hospitals [77].

Dietary protein may positively impact bone health by increasing muscle mass, increasing calcium absorption, suppressing parathyroid hormone, and increasing IGF-I production [78]. IGF-I is a potent bone anabolism stimulator. Protein intake has been correlated with markers of bone resorption: high excretion of deoxypyridinoline was associated with low dietary protein intake [79], whereas high protein intake was correlated with lower levels of urinary N-telopeptide excretion and higher levels of circulating IGF-I [80].

High protein intake may positively impact bone health by several mechanisms involving increases in IGF-I, calcitriol, intestinal calcium absorption, and urinary calcium excretion, as a consequence of increased calcium intestinal absorption, and enhancement of lean body mass, while low protein intake leads to decreases in these factors, secondary hyperparathyroidism and increased bone turnover [81]. There is some evidence that essential amino acids have a positive effect on bone formation. Higher IGF-I levels, as well as greater bone formation and reduced bone resorption as assessed by biochemical markers of bone remodelling, are found following essential amino acid supplementation [82].

In the Framingham Osteoporosis Study, mean protein intake was 68 g/d (± 24; range, 14–175 g/d), and mean percent of energy from protein was 16% (± 3; range, 7–30%) among 391 women and 224 men (mean age 75 years) [83]. Lower protein intake over 4 years was significantly associated with bone loss at the proximal femur and spine in women aged 68–91 years [83]. In a systematic review and meta-analysis, a positive association between protein intake and BMD, bone mineral content, and a reduction in bone resorption markers was found [84]. A positive association of dairy protein intake with appendicular bone mineralization and muscle mass has been found in elderly women (aged 80–92 years) [85]. Many fractures in this age group are of the appendicular skeleton, often associated with falls. The associations with bone measures were dependent on dairy protein and calcium intakes, whereas the association with appendicular muscle mass was not totally dependent on dairy protein intake. Some studies show that the positive effect of protein on bone health is augmented by increased calcium intake [78]. There is evidence that diets high in protein and dairy may help attenuate bone loss during weight loss [86]. Protein may help preserve bone mass during weight loss by stimulating IGF-I and increasing intestinal calcium absorption. However, the standard measure of BMD is dual-energy X-ray absorptiometry (DXA), which does not take into account bone microstructure. Furthermore, DXA measurement of bone area can be affected by soft tissue thickness and body composition changes, which could thus influence bone DXA assessment [86].

In terms of functional outcomes, there is only weak evidence of a possible link between protein intake and osteoporotic fracture and a lack of long-term interventional studies. There are many longitudinal/observational studies with mixed findings for either positive, negative or no association [84]. Cohort studies indicate either a benefit or no effect of protein intake on the relative risk of hip fracture. However, overall there is insufficient evidence from interventional studies to correlate high protein intake with reduced fracture risk [84]. A prospective analysis of 144,580 women aged 50–79 years included in the Women's Health Initiative has found that higher biomarker-calibrated protein intake (at 20% higher intake increments) within the range of usual intake (mean protein intake 15% of total energy intake) was inversely associated with forearm fracture and was associated with better maintenance of total and hip BMDs. These data suggest higher protein intake is not detrimental to bone health in postmenopausal women [87]. Protein intake coupled with calcium intake of 800 mg/d was shown to protect against hip fracture in the Framingham Offspring cohort, whereas the effect appeared to be reversed for those with lower calcium intake [88]. Thus, there is evidence that calcium intake modifies the association of protein intake and the risk of hip fracture, which may explain the lack of concordance seen in other studies.

A recent epidemiological study of 6381 US men and women aged ≥50 years from NHANES III has explored the link between the level and source of proteins and amino acids, ageing, diseases, and mortality [64]. Low protein intake (<10% of total kcal, or around 41 g/d) among respondents aged >65 years was associated with a 10% increased risk of cancer mortality over the following 18 years, although an inverse association was found among people aged 50–65 years [64].

5.1. Acid-ash hypothesis

There has been much focus on the 'acid-ash hypothesis', which theorizes that high protein intake (of animal origin) leads to increased acid production and increased bone resorption, leading to hypercalciuria, bone loss and osteoporosis. In support of the theory, there is limited evidence that administration of bicarbonate leads to increase in muscle performance and BMD in healthy postmenopausal women [89,90]. However, acid production is high in many non-animal protein foods and while an alkaline diet leads to an increase in urinary pH, blood pH is not affected. Thus, it is unlikely that the bone is exposed to more acid [91].

The findings of a meta-analysis do not support the concept that calciuria is associated with higher net acid excretion and reflects a net loss of whole body calcium. There is no evidence from

balance studies that increasing the diet acid load promotes skeletal bone mineral loss or osteoporosis. Changes of urine calcium do not accurately represent calcium balance. Further, a systematic review and meta-analysis has uncovered several weaknesses regarding the acid-ash hypothesis [92]. None of the intervention studies provided direct evidence of osteoporosis progression (fragility fractures, or bone strength), and the supporting prospective cohort studies were not controlled regarding important osteoporosis risk factors including: weight loss, family history of osteoporosis, baseline BMD, and oestrogen status.

Section summary:

- Dietary proteins have a direct effect on key regulatory proteins and growth factors involved in muscle and bone growth. For example, aromatic amino acids (prevalent in dairy protein) lead to increased IGF-I resulting in greater muscle mass and strength.
- Low dietary intake of protein (below the recommended daily allowance level of 0.8 g/kg/BW/d) in elderly women is associated with a reduction in plasma IGF-I levels and skeletal muscle fibre atrophy. The least muscle loss was seen in the elderly (aged 70–79 years) consuming protein at 1.1 g/kg/BW/d or 18% of total energy intake.
- The distribution of protein intake over the day may be important, and it is proposed that 20–25 g of dietary protein per meal is required to allow an appropriate stimulation of postprandial muscle protein synthesis over a 24-h period.
- Dietary protein may positively impact bone health by increasing calcium absorption, suppressing parathyroid hormone, and increasing production of IGF-I, a potent bone anabolism stimulator.
- A positive association between protein intake and BMD, bone mineral content, and a reduction in bone resorption markers has been demonstrated in a meta-analysis.
- There is no evidence to support the theory that high protein intake (of animal origin) leads to increased bone resorption, bone loss and osteoporosis.

6. Combined effect of protein intake and exercise on muscle and bone health

There is increasing evidence that bone mass and strength is related to muscle function. This intrinsic relationship between muscle and bone is described by the mechanostat theory (the combination of factors that make healthy load-bearing bones), which postulates that increasing maximal muscle force during growth or in response to increased loading will affect bone mass, size, and strength (Fig. 4) [93].

Age-related decline in muscle strength affects functional capacity, metabolic disease and QoL. Resistance exercise training is a stimulus for muscle protein synthesis, and appears to be beneficial to rebuild muscle mass, strength, and performance in the elderly. Exercise training in the elderly can lead to increased muscle mass and strength, and improved endurance and functional capacity [94]. Both aerobic activity and resistance training are demonstrated to be of benefit to older people. The American Heart Association (AHA) and the American College of Sports Medicine (ASCM) encourage older adults to accumulate 30–60 min of moderate intensity aerobic exercise per day (150–300 min/week) or 20–30 min per day of vigorous intensity exercise (75–150 min/week) [95,96]. In addition, to counteract muscle loss and increase strength, resistance exercises are strongly recommended for 2 or more non-consecutive days per week. For healthy older adults, exercise of 10–15 min per session with 8 repetitions for each muscle group is a reasonable goal.

Resistance exercise may have additional beneficial effects on bone strength. A 12-month community-based randomized controlled trial (RCT) of a progressive resistance training exercise combined with osteoporosis education and a behavioural change programme, among 162 older adults (mean age 67 years) demonstrated modest but significant net gains in femoral neck and lumbar spine BMD (1–1.1%, $p < 0.05$), muscle strength (10–13%, $p < 0.05$), functional muscle power (Timed Stair Climb, 5%, $p < 0.05$) and dynamic balance (Four Square Step Test 6%, $p < 0.01$; Sit-to-Stand, 16%, $p < 0.001$) relative to controls, although this did not translate into a reduction in the rate of falls [97,98]. Post-exercise nutrient supplementation (containing protein, carbohydrate, calcium, and vitamin D) in early postmenopausal women is associated with superior improvements in muscle mass, muscle strength, femoral neck BMD, and bone formation during 24 weeks of strength training, as compared with exercise alone [99]. A meta-analysis of RCTs examining the effect of exercise alone on lower-extremity bone strength indicated that while programmes incorporating regular weight-bearing exercise can result in 1–8% improvements in bone strength among children and adolescents, in premenopausal women with high exercise compliance improvements range from 0.5% to 2.5% [100].

Resistance exercise and amino acid availability are positive regulators of muscle protein net balance. Exercise stimulates both muscle protein synthesis as well as breakdown, albeit the latter to a

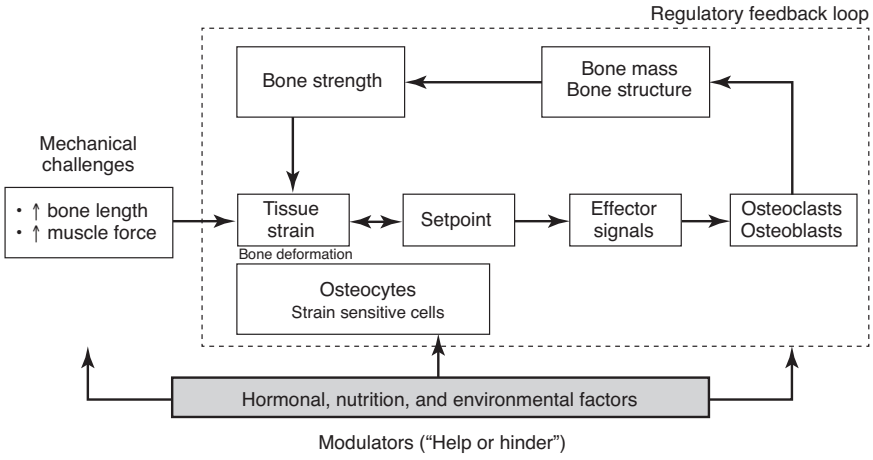

Fig. 4. Frost's mechanostat functional model of bone development and strength.
Source: Schoenau and Fricke. Eur J Endocrinol 2008;159:S27–31 [93].

lesser extent, thereby improving net protein balance. However, net muscle protein balance remains negative in the absence of nutrient intake [101]. Thus, optimal nutritional status is required to derive optimal benefit from resistance exercise training [102]. The combination of exercise followed by protein ingestion enhances muscle protein synthesis further than exercise alone and results in greater net muscle protein accretion [103,104]. Protein intake and exercise combined lead to a greater degree of muscle protein accretion than either intervention alone [105,106].

Physical activity is required before eating to improve the efficacy by which dietary protein is being used for de novo muscle protein synthesis. In contrast, physical inactivity and disuse can impair the muscle protein synthesis response to feeding and lead to rapid muscle loss [55]. The interactive effect of protein intake and exercise may be due in part to exercise-stimulated blood flow and increased amino acid delivery to the muscle [104]. Activation of the mTOR pathway by exercise may prime the muscle to respond more prominently to amino acid ingestion, although this pathway may be impaired in older adults, and the response may be somewhat delayed with ageing [107]. Positive effects of dairy proteins (whey, caseinate 0.30 g/kg lean body mass), on protein net balance, mRNA expression, and regulation of atrogene expression have been demonstrated in young healthy males after heavy resistance exercise [108].

The response to exercise training and protein supplementation is the focus of a meta-analysis that found that protein supplementation increases muscle mass and strength gains during prolonged resistance-type exercise training in both young and older subjects [109]. In young women, the consumption of dairy protein after resistance exercise supports muscle anabolism. In addition, dairy consumption after resistance exercise positively impacts on body composition by promoting losses in fat, gains or maintenance of lean mass and preservation of bone (although increases in BMD measured using DXA may occur as an artefact of the measurement method) [110,111]. Exercise and protein supplementation in frail elderly people can lead to an increase in muscle mass and an increase in strength [75]. Protein or amino acids in combination with exercise has additive effects on muscle protein synthesis in older adults, although the response may be somewhat delayed in older people [107]. Nonetheless, it has been proposed that dietary protein supplementation is required to maximize skeletal muscle mass gain during prolonged resistance-type exercise training and, as such, to more effectively counteract sarcopenia [8,112].

Section summary:

- Resistance exercise training is a stimulus for muscle protein synthesis, and appears to be beneficial to rebuild muscle mass, strength, and performance in the elderly.
- Optimal nutritional status is required to derive optimal benefit from resistance exercise training. The combination of exercise followed by protein ingestion enhances muscle protein synthesis further than exercise alone and results in greater net muscle protein accretion.
- Dairy protein consumption after resistance exercise positively impacts on body composition by promoting losses in fat, gains or maintenance of lean mass and preservation of bone.

7. Effects of vitamin D on muscle and bone

Vitamin D is known to play a role in calcium homeostasis and skeletal mineralization through endocrine effects on bone, intestine, parathyroid glands and kidney. Vitamin D insufficiency has well known direct effects on bone health, through deregulation of calcium homeostasis and increased serum parathyroid hormone, which negatively affects bone remodelling by increased bone resorption. In elderly or postmenopausal women this may exacerbate osteoporosis. Serum 25-hydroxyvitamin D (25(OH)D) levels <50 nmol/L are associated with increased bone turnover, bone loss and possibly mineralization defects, and poorer outcomes for frailty, hip fracture and all-cause mortality [23].

Vitamin D has both skeletal and extra-skeletal benefits. There is growing evidence that vitamin D regulates many other cell functions, and the potential effect of vitamin D on skeletal muscle mass and strength is receiving recent attention. The biological actions of vitamin D on muscle cell differentiation, metabolism and function may be multiple, acting through direct and indirect, genomic and non-genomic pathways. Vitamin D increases calcium uptake in muscle cells and has a regulator effect on the calcium channel, which is important for muscle contractile activity [113]. Vitamin D promotes protein synthesis and calcium and phosphate transport in muscle, thus influencing muscle strength [114]. Vitamin D appears to optimize the effect of dietary proteins on skeletal muscle anabolism. Vitamin D is demonstrated to increase muscle protein synthesis in rats with additional effects to enhance the stimulating effect of leucine and insulin on protein synthesis rate in muscle cells [115]. The identification of vitamin D receptors (VDR) in skeletal muscle cells provides evidence for a direct mechanism by which vitamin D acts on skeletal muscle [116–118].

Vitamin D deficiency is associated with a loss of muscle mass and strength in older people [119]. Vitamin D status and VDR expression in skeletal muscle are reduced in elderly people, and vitamin D deficiency in older people is associated with a significant loss of muscle function [119]. Analysis of men and women aged over 60 years who took part in the NHANES III survey found that those with higher 25(OH)D levels up to 94 nmol/L had faster gait speed and shorter sit to stand time than those with lower levels. Lower levels of serum 25(OH)D were found to be predictive of decreased grip strength and appendicular muscle mass in men and women over subsequent 3 years [120]. In addition, there is an increased risk of a decline in physical performance over 3 years in those with serum 25(OH)D <50 nmol/L as compared with those with levels ≥75 nmol/L [121], which is corroborated by findings of a recent longitudinal study [122].

Muscle strength and physical performance are linked to risk of falls in older individuals. Observational studies have shown that low 25(OH)D levels <25 nmol/L are associated with an increased risk of falls, and recurrent falls [123,124]. Replenishing vitamin D stores in an ageing population may be important for the preservation of physical function and the reduction in falls risk. Vitamin D supplementation is demonstrated to have beneficial effects on muscle health. One study has shown that vitamin D supplementation reverses muscular atrophy and increases strength in women after stroke [125]. Vitamin D supplementation improves muscle fibre cross-sectional area [126], and vitamin D supplementation with >800 IU/d significantly increases muscle strength [119,127,128]. A meta-analysis has shown that whereas vitamin D supplementation increases proximal muscle strength of the lower extremities in adults with vitamin D deficiency, it does not have a significant effect on muscle strength in adults with baseline 25(OH)D >25 nmol/L [129]. The effect of vitamin D supplementation on risk of falls is the subject of numerous meta-analyses, with some finding that vitamin D doses ranging from 700–1000 IU/d reduce the risk of falling by 14–19% [130–132]. However, others conclude that there may be no benefit on risk of falls, or only benefit in those with low vitamin D status [133,134].

Table 1
Summary of guideline recommendations for recommended dietary intakes of vitamin D and protein in women over 50 years of age.

	Institute of Medicine [61,133]		ESCEO Guidance for Elderly and Postmenopausal Women [20,23]		PROT-AGE Guidance for Older People[a] [21]
Age	Vitamin D RDA (IU/d)	Protein RDA (g/kg BW/d)[b]	Vitamin D RDI (IU/d)	Protein RDI (g/kg BW/d)	Protein RDI (g/kg BW/d)
51–70 years	600	0.8	800	1.0	1.0–1.2
70+ years	800	0.8	800	1.0	1.0–1.2
Osteoporotic patients with serum vitamin D <50 nmol/L or <75 nmol/L in elderly with a high risk of falls and fractures	n/s	0.8	800–1000	1.0	n/s

[a] PROT-AGE recommendations target older persons aged >65 years regardless of gender.
[b] Institute of Medicine advises protein RDA 0.8 g/kg BW/d in all adults regardless of age or gender, RDA, recommended daily allowance (intake that covers needs of ≥97.5% of population); RDI, recommended daily intake; n/s, not specified.

Section summary:

- Vitamin D is known to play a role in calcium homeostasis and skeletal mineralization, and serum 25(OH)D levels <50 nmol/L are associated with increased bone turnover, bone loss, and poorer outcomes for frailty and hip fracture.
- There is growing evidence that vitamin D regulates many other cell functions, and the potential effect of vitamin D on skeletal muscle mass and strength is receiving recent attention.
- Vitamin D promotes protein synthesis and calcium and phosphate transport in muscle, thus influencing muscle strength. Vitamin D deficiency is associated with a loss of muscle mass and strength in older people, and a decline in physical performance.
- Muscle strength and physical performance are linked to risk of falls in older individuals. Low 25(OH)D levels <25 nmol/L are associated with an increased risk of falls and recurrent falls. There is evidence that vitamin D supplementation (700–1000 IU/d) reduces the risk of falls by 14–19%, although the benefit may be limited to those with low vitamin D status.

8. Recommendations for optimizing musculoskeletal health

Optimal dietary intake of protein and vitamin D as well as calcium may prevent or attenuate age-related alterations in musculoskeletal health in postmenopausal women. Thus, recommendations for optimal intake should be considered. Current guidelines for dietary protein intakes have traditionally advised similar intake for all adults regardless of age or sex: 0.8 g/kg BW/d [60–62] while recent guidelines from the PROT-AGE Study Group and the European Society for Clinical Nutrition and Metabolism (ESPEN) recommend higher average daily intake in the range of 1.0–1.2 g/kg BW/d in healthy older persons aged >65 years [21,22]. Guidelines from the ESCEO propose optimized recommended nutrient intakes for calcium (1000 mg/d), vitamin D (800 IU/d) and protein (1.0–1.2 g/kg BW/d) for the general management of patients with osteoporosis [20]. In addition, the ESCEO recommends vitamin D supplementation at 800–1000 IU/d to maintain serum 25-(OH)D concentration >50 nmol/L in elderly or postmenopausal women at risk of vitamin D deficiency [23] (Table 1).

A dietary plan that includes 25–30 g of high-quality protein per meal may be considered optimal to maximize muscle protein synthesis [67]. A high-quality protein diet for older people may be defined as one that has high likelihood of promoting healthy ageing or improving age-related problems and diseases. Protein quality may be defined by essential amino acid composition, digestibility and absorption of the protein, and recognizing the role of specific amino acids in regulation of cellular processes [21]. Branched-chain amino acids including leucine have specific positive effects on signalling pathways for muscle protein synthesis [135]. From available studies, intake of 2.0–2.5 g of leucine may be beneficial to stimulate postprandial muscle protein synthesis [55,56]. Milk-derived proteins (whey, casein) are demonstrated to be more efficient for improving muscle protein synthesis than plant-derived proteins (soy proteins) [136]. Dairy products including milk, yoghourt, and cheese may represent an excellent dietary source of bone nutrients, as they provide a rich supply of calcium, phosphorus and high-quality protein at a relatively low cost [137,138].

In consideration of existing recommendations and the knowledge base on the impact of protein and vitamin D on muscle mass and strength, and bone health, the ESCEO Task Force recommends the following targets for maintaining musculoskeletal health in postmenopausal women (aged 50–70 years) in addition to adequate calcium intake (1000 mg/d):

- An average daily protein intake of 1.0–1.2 g/kg BW/d, with at least 20–25 g of high-quality protein (such as can be supplied by dairy protein) with each main meal (breakfast, lunch, dinner) during the day.
- Regular physical exercise 3–5 times per week should be undertaken, which may be combined with protein intake in proximity to exercise, for optimal muscle reconditioning.
- Vitamin D intake at 800 IU/d to maintain serum 25-(OH)D concentration >50 nmol/L (>20 ng/mL). There are three main possibilities to increase vitamin D levels: encourage increased intake of natural sources, use of fortified foods, and supplementation, which could all be combined.
- When indicated among women aged <60 years or within 10 years after menopause, HRT may be recommended for additional benefit to musculoskeletal health.

9. Conclusions

Age-related alterations in musculoskeletal health lead to reductions in muscle mass, strength and power, as well as to reductions in BMD and bone strength, which are responsible for increased fracture risk, disability, loss of independence, deteriorating QoL and increased mortality. In women, an accelerated loss of muscle mass and strength occurs at an earlier age than in men, around the time of menopause, along with a reduction in BMD which is associated with a significant increase in the prevalence of osteoporosis.

Higher protein intake (at 1.0–1.2 g/kg BW/d) and higher vitamin D supplementation levels (800–1000 IU/d) are associated with higher muscle mass, higher muscle strength and improved bone health. Evidence favouring increased protein intake above the current RDA of 0.8 g/kg/BW/d is available. The effect of protein intake

is augmented by physical activity. Vitamin D status appears to be important for dietary protein efficiency to maintain/increase muscle mass and function in older people, and future studies may better identify the role of vitamin D on muscle.

In light of existing recommendations and the knowledge base on the impact of protein and vitamin D on muscle mass, muscle strength and bone health, the ESCEO Task Force has made the recommendations summarized in the panel for maintaining musculoskeletal health in postmenopausal women (aged 50–70 years). Increased awareness of the consequences of low protein and vitamin D intakes on postmenopausal health may promote improved attitudes in women towards dietary sources and change behaviours leading to better adherence to health recommendations.

Recommendations summary

ESCEO recommendations for maintaining musculoskeletal health in postmenopausal women (aged 50–70 years)

- An average daily protein intake of 1.0–1.2 g/kg BW/d, with at least 20–25 g of high-quality protein (such as can be supplied by dairy protein) with each main meal (breakfast, lunch, dinner) during the day.
- Regular physical exercise 3–5 times per week should be undertaken, which may be combined with protein intake in proximity to exercise, for optimal muscle reconditioning.
- Vitamin D intake at 800 IU/d to maintain serum 25-(OH)D concentration >50 nmol/L (>20 ng/ml), as well as calcium (1000 mg/d).
- When indicated among women aged <60 years or within 10 years after menopause, HRT may be recommended for additional benefit to musculoskeletal health.

Contributors

All authors were fully involved in the preparation of the manuscript and take responsibility for this work. Each of the authors has read and concurs with the content in the final version.

Competing interests

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References

[1] Barry BK, Carson RG. The consequences of resistance training for movement control in older adults. J Gerontol A: Biol Sci Med Sci 2004;59:730–54.
[2] Keaveny TM, Kopperdahl DL, Melton 3rd LJ, et al. Age-dependence of femoral strength in white women and men. J Bone Miner Res 2010;25:994–1001.
[3] Cruz-Jentoft AJ, Baeyens JP, Bauer JM, et al. Sarcopenia: European consensus on definition and diagnosis: Report of the European Working Group on Sarcopenia in Older People. Age Ageing 2010;39:412–23.
[4] Hernlund E, Svedbom A, Ivergard M, et al. Osteoporosis in the European Union: Medical Management, Epidemiology and Economic Burden. A report prepared in collaboration with the International Osteoporosis Foundation (IOF) and the European Federation of Pharmaceutical Industry Associations (EFPIA). Arch Osteoporos 2013;8:136, http://dx.doi.org/10.1007/s11657-013-0136-1.
[5] Maltais ML, Desroches J, Dionne IJ. Changes in muscle mass and strength after menopause. J Musculoskelet Neuronal Interact 2009;9:186–97.
[6] Walrand S, Guillet C, Salles J, et al. Physiopathological mechanism of sarcopenia. Clin Geriatr Med 2011;27:365–85.
[7] Patel HP, Syddall HE, Jameson K, et al. Prevalence of sarcopenia in community-dwelling older people in the UK using the European Working Group on Sarcopenia in Older People (EWGSOP) definition: findings from the Hertfordshire Cohort Study (HCS). Age Ageing 2013;42:378–84.
[8] Fielding RA, Vellas B, Evans WJ, et al. Sarcopenia: an undiagnosed condition in older adults. Current consensus definition: prevalence, etiology, and consequences. International working group on sarcopenia. J Am Med Dir Assoc 2011;12:249–56.
[9] Cooper C, Fielding R, Visser M, et al. Tools in the assessment of sarcopenia. Calcif Tissue Int 2013;93:201–10.
[10] Muscaritoli M, Anker SD, Argiles J, et al. Consensus definition of sarcopenia, cachexia and pre-cachexia: joint document elaborated by Special Interest Groups (SIG) cachexia-anorexia in chronic wasting diseases and nutrition in geriatrics. Clin Nutr 2010;29:154–9.
[11] Baumgartner RN, Koehler KM, Gallagher D, et al. Epidemiology of sarcopenia among the elderly in New Mexico. Am J Epidemiol 1998;147:755–63.
[12] Morley JE, Baumgartner RN, Roubenoff R, et al. Sarcopenia. J Lab Clin Med 2001;137:231–43.
[13] Janssen I, Heymsfield SB, Ross R. Low relative skeletal muscle mass (sarcopenia) in older persons is associated with functional impairment and physical disability. J Am Geriatr Soc 2002;50:889–96.
[14] Janssen I, Shepard DS, Katzmarzyk PT, Roubenoff R. The healthcare costs of sarcopenia in the United States. J Am Geriatr Soc 2004;52:80–5.
[15] Stevenson JC. A woman's journey through the reproductive, transitional and postmenopausal periods of life: impact on cardiovascular and musculo-skeletal risk and the role of estrogen replacement. Maturitas 2011;70:197–205.
[16] WHO. Facts about ageing. World Health Organization; 2012 http://www.who.int/ageing/about/facts/en/index.html
[17] Ferrucci L, Baroni M, Ranchelli A, et al. Interaction between bone and muscle in older persons with mobility limitations. Curr Pharm Des 2014;20:3178–97.
[18] Robinson S, Cooper C, Aihie Sayer A. Nutrition and sarcopenia: a review of the evidence and implications for preventive strategies. J Aging Res 2012;2012:510801, http://dx.doi.org/10.1155/2012/510801 [Epub 15.03.12].
[19] Sayer AA, Robinson SM, Patel HP, et al. New horizons in the pathogenesis, diagnosis and management of sarcopenia. Age Ageing 2013;42:145–50.
[20] Kanis JA, McCloskey EV, Johansson H, et al. European guidance for the diagnosis and management of osteoporosis in postmenopausal women. Osteoporos Int 2013;24:23–57.
[21] Bauer J, Biolo G, Cederholm T, et al. Evidence-based recommendations for optimal dietary protein intake in older people: a position paper from the PROT-AGE Study Group. J Am Med Dir Assoc 2013;14:542–59.
[22] Deutz NE, Bauer JM, Barazzoni R, et al. Protein intake and exercise for optimal muscle function with aging: recommendations from the ESPEN Expert

Group. Clin Nutr 2014;April, http://dx.doi.org/10.1016/j.clnu.2014.04.007. pii:S0261-5614(14)00111-3.
[23] Rizzoli R, Boonen S, Brandi ML, et al. Vitamin D supplementation in elderly or postmenopausal women: a 2013 update of the 2008 recommendations from the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO). Curr Med Res Opin 2013;29:305–13.
[24] Novak LP. Aging, total body potassium, fat-free mass, and cell mass in males and females between ages 18 and 85 years. J Gerontol 1972;27:438–43.
[25] Kyle UG, Genton L, Slosman DO, Pichard C. Fat-free and fat mass percentiles in 5225 healthy subjects aged 15–98 years. Nutrition 2001;17:534–41.
[26] Ley CJ, Lees B, Stevenson JC. Sex- and menopause-associated changes in body-fat distribution. Am J Clin Nutr 1992;55:950–4.
[27] Nilwik R, Snijders T, Leenders M, et al. The decline in skeletal muscle mass with aging is mainly attributed to a reduction in type II muscle fiber size. Exp Gerontol 2013;48:492–8.
[28] von Haehling S, Morley JE, Anker SD. From muscle wasting to sarcopenia and myopenia: update 2012. J Cachexia Sarcopenia Muscle 2012;3:213–7.
[29] Leenders M, Verdijk LB, van der Hoeven L, et al. Patients with type 2 diabetes show a greater decline in muscle mass, muscle strength, and functional capacity with aging. J Am Med Dir Assoc 2013;14:585–92.
[30] Koster A, Visser M, Simonsick EM, et al. Association between fitness and changes in body composition and muscle strength. J Am Geriatr Soc 2010;58:219–26.
[31] Janssen I, Baumgartner RN, Ross R, et al. Skeletal muscle cutpoints associated with elevated physical disability risk in older men and women. Am J Epidemiol 2004;159:413–21.
[32] Koopman R, van Loon LJ. Aging exercise, and muscle protein metabolism. J Appl Physiol (1985) 2009;106:2040–8.
[33] Ferrucci L, de Cabo R, Knuth ND, Studenski S. Of Greek heroes, wiggling worms, mighty mice, and old body builders. J Gerontol A: Biol Sci Med Sci 2011;67A:13–6.
[34] Manini TM, Russ DW, Clark BC. In: Cruz-Jentoft AJ, Morley JE, editors. The complex relation between muscle mass and muscle strength. Sarcopenia, London: John Wiley & Sons Ltd.; 2012. p. 74–103.
[35] Ko Su Hausdorff JM, Ferrucci L. Age-associated differences in the gait pattern changes of older adults during fast-speed and fatigue conditions: results from the Baltimore longitudinal study of ageing. Age Ageing 2010;39:688–94.
[36] Studenski S, Perera S, Patel K, et al. Gait speed and survival in older adults. JAMA 2011;305:50–8.
[37] Stevenson JC, Lees B, Devenport M, et al. Determinants of bone density in normal women: risk factors for future osteoporosis? BMJ 1989;298:924–8.
[38] Hillard TC, Whitcroft SJ, Marsh MS, et al. Long-term effects of transdermal and oral hormone replacement therapy on postmenopausal bone loss. Osteoporos Int 1994;4:341–8.
[39] Cauley JA, Robbins J, Chen Z, et al. Effects of estrogen plus progestin on risk of fracture and bone mineral density: the Women's Health Initiative randomized trial. JAMA 2003;290:1729–38.
[40] de Villiers TJ, Pines A, Panay N, et al. Updated 2013 International Menopause Society recommendations on menopausal hormone therapy and preventive strategies for midlife health. Climacteric 2013;16:316–37.
[41] Panay N, Hamoda H, Arya R, Savvas M. The 2013 British Menopause Society & Women's Health Concern recommendations on hormone replacement therapy. Menopause Int 2013;19:59–68.
[42] Gompel A, Rozenberg S, Barlow DH. The EMAS 2008 update on clinical recommendations on postmenopausal hormone replacement therapy. Maturitas 2008;61:227–32.
[43] Lowe DA, Baltgalvis KA, Greising SM. Mechanisms behind estrogen's beneficial effect on muscle strength in females. Exerc Sport Sci Rev 2010;38:61–7.
[44] Phillips SK, Rook KM, Siddle NC, et al. Muscle weakness in women occurs at an earlier age than in men, but strength is preserved by hormone replacement therapy. Clin Sci (Lond) 1993;84:95–8.
[45] Ronkainen PH, Kovanen V, Alen M, et al. Postmenopausal hormone replacement therapy modifies skeletal muscle composition and function: a study with monozygotic twin pairs. J Appl Physiol (1985) 2009;107:25–33.
[46] Qaisar R, Renaud G, Hedstrom Y, et al. Hormone replacement therapy improves contractile function and myonuclear organization of single muscle fibres from postmenopausal monozygotic female twin pairs. J Physiol 2013;591:2333–44.
[47] Short KR, Vittone JL, Bigelow ML, et al. Age and aerobic exercise training effects on whole body and muscle protein metabolism. Am J Physiol Endocrinol Metab 2004;286:E92–101.
[48] Volpi E, Sheffield-Moore M, Rasmussen BB, Wolfe RR. Basal muscle amino acid kinetics and protein synthesis in healthy young and older men. JAMA 2001;286:1206–12.
[49] Moreau K, Walrand S, Boirie Y. Protein redistribution from skeletal muscle to splanchnic tissue on fasting and refeeding in young and older healthy individuals. J Am Med Dir Assoc 2013;14:696–704.
[50] Rennie MJ, Edwards RH, Halliday D, et al. Muscle protein synthesis measured by stable isotope techniques in man: the effects of feeding and fasting. Clin Sci (Lond) 1982;63:519–23.
[51] Cuthbertson D, Smith K, Babraj J, et al. Anabolic signaling deficits underlie amino acid resistance of wasting, aging muscle. FASEB J 2005;19:422–4.
[52] Burd NA, Gorissen SH, van Loon LJ. Anabolic resistance of muscle protein synthesis with aging. Exerc Sport Sci Rev 2013;41:169–73.
[53] Pennings B, Groen B, de Lange A, et al. Amino acid absorption and subsequent muscle protein accretion following graded intakes of whey protein in elderly men. Am J Physiol Endocrinol Metab 2012;302:E992–9.
[54] Pennings B, Boirie Y, Senden JM, et al. Whey protein stimulates postprandial muscle protein accretion more effectively than do casein and casein hydrolysate in older men. Am J Clin Nutr 2011;93:997–1005.
[55] Wall BT, Hamer HM, de Lange A, et al. Leucine co-ingestion improves post-prandial muscle protein accretion in elderly men. Clin Nutr 2013;32:412–9.
[56] Yang Y, Breen L, Burd NA, et al. Resistance exercise enhances myofibrillar protein synthesis with graded intakes of whey protein in older men. Br J Nutr 2012;108:1780–8.
[57] Timmerman KL, Volpi E. Amino acid metabolism and regulatory effects in aging. Curr Opin Clin Nutr Metab Care 2008;11:45–9.
[58] Dawson-Hughes B, Harris SS, Rasmussen HM, Dallal GE. Comparative effects of oral aromatic and branched-chain amino acids on urine calcium excretion in humans. Osteoporos Int 2007;18:955–61.
[59] Bonjour JP, Kraenzlin M, Levasseur R, et al. Dairy in adulthood: from foods to nutrient interactions on bone and skeletal muscle health. J Am Coll Nutr 2013;32:251–63.
[60] WHO. Protein and amino acid requirements in human nutrition: report of a joint WHO/FAO/UNU expert consultation. Geneva; 2007.
[61] IoM. Dietary Reference Intakes for energy, carbohydrate, fiber, fat fatty acids, cholesterol, protein, and amino acids (macronutrients). Washington, DC; 2005.
[62] EFSA. Outcome of a public consultation on the draft scientific opinion of the EFSA Panel on Dietetic Products, Nutrition, and Allergies (NDA) on dietary reference values for protein. Parma, Italy; 2012.
[63] Castaneda C, Gordon PL, Fielding RA, et al. Marginal protein intake results in reduced plasma IGF-I levels and skeletal muscle fiber atrophy in elderly women. J Nutr Health Aging 2000;4:85–90.
[64] Levine ME, Suarez JA, Brandhorst S, et al. Low protein intake is associated with a major reduction in IGF-1, cancer, and overall mortality in the 65 and younger but not older population. Cell Metab 2014;19:407–17.
[65] Fulgoni 3rd VL. Current protein intake in America: analysis of the National Health and Nutrition Examination Survey, 2003–2004. Am J Clin Nutr 2008;87:1554S–7S.
[66] Tieland M, Borgonjen-Van den Berg KJ, van Loon LJ, de Groot LC. Dietary protein intake in community-dwelling, frail, and institutionalized elderly people: scope for improvement. Eur J Nutr 2012;51:173–9.
[67] Paddon-Jones D, Rasmussen BB. Dietary protein recommendations and the prevention of sarcopenia. Curr Opin Clin Nutr Metab Care 2009;12:86–90.
[68] Mamerow MM, Mettler JA, English KL, et al. Dietary protein distribution positively influences 24-h muscle protein synthesis in healthy adults. J Nutr 2014;144:876–80.
[69] Bouillanne O, Curis E, Hamon-Vilcot B, et al. Impact of protein pulse feeding on lean mass in malnourished and at-risk hospitalized elderly patients: a randomized controlled trial. Clin Nutr 2013;32:186–92.
[70] Paddon-Jones D, Leidy H. Dietary protein and muscle in older persons. Curr Opin Clin Nutr Metab Care 2014;17:5–11.
[71] Houston DK, Nicklas BJ, Ding J, et al. Dietary protein intake is associated with lean mass change in older, community-dwelling adults: the Health, Aging, and Body Composition (Health ABC) Study. Am J Clin Nutr 2008;87:150–5.
[72] Meng X, Zhu K, Devine A, et al. A 5-year cohort study of the effects of high protein intake on lean mass and BMC in elderly postmenopausal women. J Bone Miner Res 2009;24:1827–34.
[73] Beasley JM, Wertheim BC, LaCroix AZ, et al. Biomarker-calibrated protein intake and physical function in the Women's Health Initiative. J Am Geriatr Soc 2013;61:1863–71.
[74] Tieland M, van de Rest O, Dirks ML, et al. Protein supplementation improves physical performance in frail elderly people: a randomized, double-blind, placebo-controlled trial. J Am Med Dir Assoc 2012;13:720–6.
[75] Tieland M, Dirks ML, van der Zwaluw N, et al. Protein supplementation increases muscle mass gain during prolonged resistance-type exercise training in frail elderly people: a randomized, double-blind, placebo-controlled trial. J Am Med Dir Assoc 2012;13:713–9.
[76] Kim CO, Lee KR. Preventive effect of protein-energy supplementation on the functional decline of frail older adults with low socioeconomic status: a community-based randomized controlled study. J Gerontol A: Biol Sci Med Sci 2013;68:309–16.
[77] Schurch MA, Rizzoli R, Slosman D, et al. Protein supplements increase serum insulin-like growth factor-I levels and attenuate proximal femur bone loss in patients with recent hip fracture. A randomized, double-blind, placebo-controlled trial. Ann Intern Med 1998;128:801–9.
[78] Mangano KM, Sahni S, Kerstetter JE. Dietary protein is beneficial to bone health under conditions of adequate calcium intake: an update on clinical research. Curr Opin Clin Nutr Metab Care 2014;17:69–74.
[79] Macdonald HM, New SA, Fraser WD, et al. Low dietary potassium intakes and high dietary estimates of net endogenous acid production are associated with low bone mineral density in premenopausal women and increased markers of bone resorption in postmenopausal women. Am J Clin Nutr 2005;81:923–33.
[80] Dawson-Hughes B, Harris SS, Rasmussen H, et al. Effect of dietary protein supplements on calcium excretion in healthy older men and women. J Clin Endocrinol Metab 2004;89:1169–73.
[81] Kerstetter JE, Kenny AM, Insogna KL. Dietary protein and skeletal health: a review of recent human research. Curr Opin Lipidol 2011;22:16–20.

[82] Ammann P, Laib A, Bonjour JP, et al. Dietary essential amino acid supplements increase bone strength by influencing bone mass and bone microarchitecture in ovariectomized adult rats fed an isocaloric low-protein diet. J Bone Miner Res 2002;17:1264–72.
[83] Hannan MT, Tucker KL, Dawson-Hughes B, et al. Effect of dietary protein on bone loss in elderly men and women: the Framingham Osteoporosis Study. J Bone Miner Res 2000;15:2504–12.
[84] Darling AL, Millward DJ, Torgerson DJ, et al. Dietary protein and bone health: a systematic review and meta-analysis. Am J Clin Nutr 2009;90:1674–92.
[85] Radavelli-Bagatini S, Zhu K, Lewis JR, Prince RL. Dairy food intake, peripheral bone structure and muscle mass in elderly ambulatory women. J Bone Miner Res 2014, http://dx.doi.org/10.1002/jbmr.2181 [Epub 20.01.14].
[86] Tang M, O'Connor LE, Campbell WW. Diet-induced weight loss: the effect of dietary protein on bone. J Acad Nutr Diet 2014;114:72–85.
[87] Beasley JM, Lacroix AZ, Larson JC, et al. Biomarker-calibrated protein intake and bone health in the Women's Health Initiative clinical trials and observational study. Am J Clin Nutr 2014;99:934–40.
[88] Sahni S, Cupples LA, McLean RR, et al. Protective effect of high protein and calcium intake on the risk of hip fracture in the Framingham offspring cohort. J Bone Miner Res 2010;25:2770–6.
[89] Dawson-Hughes B, Castaneda-Sceppa C, Harris SS, et al. Impact of supplementation with bicarbonate on lower-extremity muscle performance in older men and women. Osteoporos Int 2010;21:1171–9.
[90] Jehle S, Hulter HN, Krapf R. Effect of potassium citrate on bone density, microarchitecture, and fracture risk in healthy older adults without osteoporosis: a randomized controlled trial. J Clin Endocrinol Metab 2013;98:207–17.
[91] Buclin T, Cosma M, Appenzeller M, et al. Diet acids and alkalis influence calcium retention in bone. Osteoporos Int 2001;12:493–9.
[92] Fenton TR, Tough SC, Lyon AW, et al. Causal assessment of dietary acid load and bone disease: a systematic review & meta-analysis applying Hill's epidemiologic criteria for causality. Nutr J 2011;10:41.
[93] Schoenau E, Fricke O. Mechanical influences on bone development in children. Eur J Endocrinol 2008;159(Suppl. 1):S27–31.
[94] Leenders M, Verdijk LB, van der Hoeven L, et al. Elderly men and women benefit equally from prolonged resistance-type exercise training. J Gerontol A: Biol Sci Med Sci 2013;68:769–79.
[95] Nelson ME, Rejeski WJ, Blair SN, et al. Physical activity and public health in older adults: recommendation from the American College of Sports Medicine and the American Heart Association. Circulation 2007;116:1094–105.
[96] Chodzko-Zajko WJ, Proctor DN, Fiatarone Singh MA, et al. American College of Sports Medicine position stand. Exercise and physical activity for older adults. Med Sci Sports Exerc 2009;41:1510–30.
[97] Gianoudis J, Bailey CA, Sanders KM, et al. Osteo-cise: Strong Bones for Life: protocol for a community-based randomised controlled trial of a multi-modal exercise and osteoporosis education program for older adults at risk of falls and fractures. BMC Musculoskelet Disord 2012;13:78.
[98] Gianoudis J, Bailey CA, Ebeling PR, et al. Effects of a targeted multimodal exercise program incorporating high-speed power training on falls and fracture risk factors in older adults: a community-based randomized controlled trial. J Bone Miner Res 2014;29:182–91.
[99] Holm L, Olesen JL, Matsumoto K, et al. Protein-containing nutrient supplementation following strength training enhances the effect on muscle mass, strength, and bone formation in postmenopausal women. J Appl Physiol (1985) 2008;105:274–81.
[100] Nikander R, Sievanen H, Heinonen A, et al. Targeted exercise against osteoporosis: a systematic review and meta-analysis for optimising bone strength throughout life. BMC Med 2010;8:47.
[101] Biolo G, Maggi SP, Williams BD, et al. Increased rates of muscle protein turnover and amino acid transport after resistance exercise in humans. Am J Physiol 1995;268:E514–20.
[102] Mithal A, Bonjour JP, Boonen S, et al. Impact of nutrition on muscle mass, strength, and performance in older adults. Osteoporos Int 2013;24:1555–66.
[103] Tang JE, Manolakos JJ, Kujbida GW, et al. Minimal whey protein with carbohydrate stimulates muscle protein synthesis following resistance exercise in trained young men. Appl Physiol Nutr Metab 2007;32:1132–8.
[104] Biolo G, Tipton KD, Klein S, Wolfe RR. An abundant supply of amino acids enhances the metabolic effect of exercise on muscle protein. Am J Physiol 1997;273:E122–9.
[105] Moore DR, Tang JE, Burd NA, et al. Differential stimulation of myofibrillar and sarcoplasmic protein synthesis with protein ingestion at rest and after resistance exercise. J Physiol 2009;587:897–904.
[106] Pennings B, Koopman R, Beelen M, et al. Exercising before protein intake allows for greater use of dietary protein-derived amino acids for de novo muscle protein synthesis in both young and elderly men. Am J Clin Nutr 2011;93:322–31.
[107] Drummond MJ, Dreyer HC, Pennings B, et al. Skeletal muscle protein anabolic response to resistance exercise and essential amino acids is delayed with aging. J Appl Physiol (1985) 2008;104:1452–61.
[108] Reitelseder S, Agergaard J, Doessing S, et al. Positive muscle protein net balance and differential regulation of atrogene expression after resistance exercise and milk protein supplementation. Eur J Nutr 2014;53:321–33.
[109] Cermak NM, Res PT, de Groot LC, et al. Protein supplementation augments the adaptive response of skeletal muscle to resistance-type exercise training: a meta-analysis. Am J Clin Nutr 2012;96:1454–64.
[110] Josse AR, Tang JE, Tarnopolsky MA, Phillips SM. Body composition and strength changes in women with milk and resistance exercise. Med Sci Sports Exerc 2010;42:1122–30.
[111] Josse AR, Phillips SM. Impact of milk consumption and resistance training on body composition of female athletes. Med Sport Sci 2012;59:94–103.
[112] Rolland Y, Dupuy C, van Kan Abellan G, et al. Treatment strategies for sarcopenia and frailty. Med Clin North Am 2011;95:427–38, ix.
[113] Morelli S, de Boland AR, Boland RL. Generation of inositol phosphates, diacylglycerol and calcium fluxes in myoblasts treated with 1,25-dihydroxyvitamin D_3. Biochem J 1993;289(Pt 3):675–9.
[114] Pfeifer M, Begerow B, Minne HW. Vitamin D and muscle function. Osteoporos Int 2002;13:187–94.
[115] Salles J, Chanet A, Giraudet C, et al. 1,25$(OH)_2$-vitamin D_3 enhances the stimulating effect of leucine and insulin on protein synthesis rate through Akt/PKB and mTOR mediated pathways in murine C2C12 skeletal myotubes. Mol Nutr Food Res 2013;57:2137–46.
[116] Simpson RU, Thomas GA, Arnold AJ. Identification of 1,25-dihydroxyvitamin D_3 receptors and activities in muscle. J Biol Chem 1985;260:8882–91.
[117] Bischoff HA, Borchers M, Gudat F, et al. In situ detection of 1,25-dihydroxyvitamin D_3 receptor in human skeletal muscle tissue. Histochem J 2001;33:19–24.
[118] Bischoff-Ferrari HA, Borchers M, Gudat F, et al. Vitamin D receptor expression in human muscle tissue decreases with age. J Bone Miner Res 2004;19:265–9.
[119] Bischoff-Ferrari HA, Dietrich T, Orav EJ, et al. Higher 25-hydroxyvitamin D concentrations are associated with better lower-extremity function in both active and inactive persons aged > or =60 y. Am J Clin Nutr 2004;80:752–8.
[120] Visser M, Deeg DJ, Lips P. Low vitamin D and high parathyroid hormone levels as determinants of loss of muscle strength and muscle mass (sarcopenia): the Longitudinal Aging Study Amsterdam. J Clin Endocrinol Metab 2003;88:5766–72.
[121] Wicherts IS, van Schoor NM, Boeke AJ, et al. Vitamin D status predicts physical performance and its decline in older persons. J Clin Endocrinol Metab 2007;92:2058–65.
[122] Houston DK, Tooze JA, Neiberg RH, et al. 25-Hydroxyvitamin D status and change in physical performance and strength in older adults: the Health, Aging, and Body Composition Study. Am J Epidemiol 2012;176:1025–34.
[123] Faulkner KA, Cauley JA, Zmuda JM, et al. Higher 1,25-dihydroxyvitamin D_3 concentrations associated with lower fall rates in older community-dwelling women. Osteoporos Int 2006;17:1318–28.
[124] Snijder MB, van Schoor NM, Pluijm SM, et al. Vitamin D status in relation to one-year risk of recurrent falling in older men and women. J Clin Endocrinol Metab 2006;91:2980–5.
[125] Sato Y, Iwamoto J, Kanoko T, Satoh K. Low-dose vitamin D prevents muscular atrophy and reduces falls and hip fractures in women after stroke: a randomized controlled trial. Cerebrovasc Dis 2005;20:187–92.
[126] Ceglia L, Niramitmahapanya S, da Silva Morais M, et al. A randomized study on the effect of vitamin D_3 supplementation on skeletal muscle morphology and vitamin D receptor concentration in older women. J Clin Endocrinol Metab 2013;98:E1927–35.
[127] Glerup H, Mikkelsen K, Poulsen L, et al. Hypovitaminosis D myopathy without biochemical signs of osteomalacic bone involvement. Calcif Tissue Int 2000;66:419–24.
[128] Muir SW, Montero-Odasso M. Effect of vitamin D supplementation on muscle strength, gait and balance in older adults: a systematic review and meta-analysis. J Am Geriatr Soc 2011;59:2291–300.
[129] Stockton KA, Mengersen K, Paratz JD, et al. Effect of vitamin D supplementation on muscle strength: a systematic review and meta-analysis. Osteoporos Int 2011;22:859–71.
[130] Michael YL, Whitlock EP, Lin JS, et al. Primary care-relevant interventions to prevent falling in older adults: a systematic evidence review for the U.S. Preventive Services Task Force. Ann Intern Med 2010;153:815–25.
[131] Murad MH, Elamin KB, Abu Elnour NO, et al. Clinical review: the effect of vitamin D on falls: a systematic review and meta-analysis. J Clin Endocrinol Metab 2011;96:2997–3006.
[132] Bischoff-Ferrari HA, Dawson-Hughes B, Staehelin HB, et al. Fall prevention with supplemental and active forms of vitamin D: a meta-analysis of randomised controlled trials. BMJ 2009;339:b3692.
[133] Ross AC, Manson JE, Abrams SA, et al. The 2011 report on dietary reference intakes for calcium and vitamin D from the Institute of Medicine: what clinicians need to know. J Clin Endocrinol Metab 2011;96:53–8.
[134] Gillespie LD, Robertson MC, Gillespie WJ, et al. Interventions for preventing falls in older people living in the community. Cochrane Database Syst Rev 2009:CD007146.
[135] Katsanos CS, Kobayashi H, Sheffield-Moore M, et al. A high proportion of leucine is required for optimal stimulation of the rate of muscle protein synthesis by essential amino acids in the elderly. Am J Physiol Endocrinol Metab 2006;291:E381–7.
[136] Phillips SM, Tang JE, Moore DR. The role of milk- and soy-based protein in support of muscle protein synthesis and muscle protein accretion in young and elderly persons. J Am Coll Nutr 2009;28:343–54.
[137] Caroli A, Poli A, Ricotta D, et al. Invited review: dairy intake and bone health: a viewpoint from the state of the art. J Dairy Sci 2011;94:5249–62.
[138] Rizzoli R. Dairy products, yogurts, and bone health. Am J Clin Nutr 2014;99:1256S–62S.