Drugs
https://doi.org/10.1007/s40265-024-02138-w

REVIEW ARTICLE

Treatment of Osteoporosis and Osteoarthritis in the Oldest Old

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Accepted: 1 December 2024

Abstract

Osteoporosis and osteoarthritis are key diseases of musculoskeletal ageing and are increasing in prevalence and burden with the progressively ageing population worldwide. These conditions are thus particularly common in 'the oldest old', and there are complexities of managing them within the context of extensive multimorbidity, physical and mental disability, and polypharmacy, the rates for all of which are high in this population. In this narrative review, we explore the epidemiology of osteoporosis and osteoarthritis in the oldest old before examining trials and real-world data relating to the pharmacological treatment of these diseases in older adults, including anti-resorptives and bone-forming agents in osteoporosis and symptomatic slow-acting drugs for osteoarthritis, paracetamol, and non-steroidal anti-inflammatory drugs in osteoarthritis, recognising that the oldest old are usually excluded from clinical trials. We then review the potential benefits of nutritional interventions and exercise therapy before highlighting the health economic benefits of interventions for osteoporosis and osteoarthritis. The high prevalence of risk factors for both disease and adverse events associated with treatment in the oldest old mean that careful attention must be paid to the potential benefits of intervention (including fracture risk reduction and improvements in osteoarthritis pain and function) versus the potential harms and adverse effects. Further direct evidence relating to such interventions is urgently needed from future research.

Key Points

The numbers of 'the oldest old' are set to rise over the coming years, and with this the burden of osteoporosis and osteoarthritis will expand.

At present, evidence for treatments for osteoporosis and osteoarthritis is lacking in this age group (with post hoc analysis playing a major role in demonstrating fracture risk reduction efficacy in anti-osteoporosis medications) and should be the subject of a future research agenda, including clinical trials.

1 Introduction

Advances in health and social care have led to a global increase in the proportion of individuals surviving into older age.

Osteoarthritis and osteoporosis were previously thought to be mutually exclusive, but this relationship has since been questioned, and further research has highlighted some shared associations and co-existence [1]. Both osteoarthritis and osteoporosis are associated with an increasing prevalence with age and so present a particular burden in older adults [2–4]. They cause substantial morbidity for individual patients and substantial financial burden for the health economy at large [5, 6].

Ageing is associated with alterations in physiology that alter the presentation of diseases and the physiological capacity to respond to interventions. Age-related changes in pharmacokinetics and pharmacodynamics

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Published online: 19 February 2025

are well-established [7], such that a tailored regulatory approach has been developed for the assessment of new medications in this age group [8, 9].

Within the cohort of ageing older adults sits a subgroup of 'the oldest old' [10]. The definition of this term is debated, but with the expansion of the ageing population, and the consequent increase in diseases of musculoskeletal ageing, there is a clear need for a robust review of interventions for osteoarthritis and osteoporosis in this group. To address this need, The European Society for the Clinical and Health Economic aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Disorders (ESCEO) convened an expert working group in February 2024. This group included patients, geriatricians, rheumatologists, orthopaedic surgeons, researchers, regulatory experts, and health economists with oral presentations of the latest literature and discussion to determine a group consensus. This is presented in the following narrative review.

2 Definition of the Oldest Old Population

The phrase 'the oldest old' refers to the oldest subset of older adults and emphasises a group of patients that may have substantial differences in pharmacokinetics and higher concurrent levels of comorbidity and who are often excluded from participating in randomised controlled trials. Chronological age cut-off values for this group vary.

For example, the European Medicines Agency sub-categorises older adults into 65–74 years for the 'young old', 75–84 years as 'middle old', and ≥ 85 years as 'oldest old' [11]. The latter is the same as the British Geriatrics Society threshold; however, The American Geriatrics Society and World Health Organization set a chronological threshold at ≥ 80 years [12]. Some individual studies choose a higher threshold of ≥ 90 years [13].

The term 'the oldest old' is sometimes used in conjunction with 'the fourth age'. Old age classically commences at 60–65 years because this is a common time for retirement from employment and has been referred to as 'the third age' [14]. The fourth age marks a move into 'dependence' and is thus used in similar context to 'the oldest old' [14].

When considering clinical practice, in some countries, older adults are admitted to a geriatric unit at the age of 80 years; however, the age of admission to such services has crept up (from ≥ 75 years) over the last 10 years and may be more due to stretched geriatric healthcare resources than to a clinically meaningful threshold.

Indeed, it is arguable that chronological age is limited in its application to the issue at hand and that measures of 'biological age' [15–17] would be more accurate in identifying individuals who display the characteristics that are most associated with 'the oldest old' (greater morbidity, higher levels of dependence, higher risk of death) but without the bias of 'ageism'; however, measures of biological age are not available in clinical practice.

It is therefore apparent that a universal definition of 'the oldest old' is yet to be reached; however, in this review, we investigate the literature relating to those (chronologically) aged ≥ 80 years, albeit focusing on as old an age group as possible (within the confines of the currently available evidence).

2.1 Osteoporosis

The operational definition of osteoporosis rests upon the measurement of bone mineral density (BMD; via dual-energy X-ray absorptiometry [DXA]) [18], which varies across the lifecourse, reaching a peak in early adulthood during the fourth decade, plateauing in middle life, and then declining from the age of 50 years. There is an increase in the incidence of all major fracture types (hip, vertebral, distal radial, proximal humerus) with age, with a near exponential increase in hip fracture incidence in men and women beyond 75 years [3]; indeed, the median age for hip fracture is well above 80 years in many countries [19]. Although, in this study, vertebral fracture incidence was not included above the age of 75 years, a similar pattern of increasing incidence is observed for vertebral fractures in other studies [20].

Epidemiological trends for fractures vary according to type of fracture. For example, data from Tottori (Japan) demonstrate an exponential increase in the incidence of fractures of the femoral neck and trochanter with increasing age, reaching an incidence of 700/100,000 person-years for femoral neck fractures and 1700/100,000 person-years for trochanteric fracture in women aged 85–90 years between 2004 and 2006 [21]. The incidence is lower in men: approximately 300/100,000 person-years for femoral neck and 600/100,000 person-years for trochanteric fracture over the same period [21]. There is variation in the distribution of incidence by age. The numbers of trochanteric fractures increase fairly rapidly from the age of 75 years, and fractures of the femoral neck exhibit a more constant, almost linear, increase in incidence from the age of 65 years [21, 22]. A recent extension of this study has demonstrated that the exponential increase in trochanteric fractures continues in the 10th decade of life (those aged 90–100 years) with an incidence of over 2000/100,000 person-years in women and approximately 1000/100,000 person-years in men [22]. Fractures are also associated with substantial increases in mortality [23, 24].

Concerningly, given the above epidemiology, which emphasises the particular burden of fractures in the oldest old, there is recognised undertreatment for those requiring

anti-osteoporosis medication in this population [25]. A study from the Newcastle 85+ cohort showed that, of 259 older adults (mean age 85.5 years, all participants were born in 1921) identified as requiring treatment for osteoporosis (via fracture risk calculation), only 74 (28.6%) were receiving anti-osteoporosis medication [26]. This represents a treatment gap of 71.4%, higher than the UK national average of 66% and emphasising the neglect that the oldest old are experiencing when it comes to osteoporosis care [27]. The issue of health equity runs deeper than the treatment gap, with a relative paucity of research into osteoporosis in older adults, leading to calls for more evidence from the International Conference on Frailty and Sarcopenia Research, which is echoed by the authors of this article [28].

2.2 Osteoarthritis

Osteoarthritis is a disease of the joint characterised by a reduction of cartilage thickness and is associated with pain, loss of function, and reduced quality of life. The robust mapping of the epidemiology of osteoarthritis is hampered, in part, by variations in disease definitions [29]. Osteoarthritis can be defined clinically (by the presence of clinician-elicited signs) [30], radiographically (by features on radiograph images) [31], or via patient self-report of prior diagnosis (e.g., via a questionnaire assessment in a cohort study). It is worth considering that the clinical diagnosis of osteoarthritis includes measures of pain and discomfort and, given that activity levels are lower in the oldest old, the degree of movement-induced pain [32] (or any pain at rest that is precipitated by preceding physical activity) may be less, potentially leading to artificially lower rates of diagnosis in this population.

The epidemiology of osteoarthritis was investigated in the 2021 Global Burden of Disease study, which estimated the global prevalence of osteoarthritis at 595 million (95% uncertainty interval [UI] 535–656) or 7.6% (95% UI 6.8–8.4) of the global population [2]. The prevalence had grown 132% (95% UI 130.3–134.1) since the year 1990, demonstrating a striking upward trajectory with a projected increase of 60–100% (depending on the site of osteoarthritis) by the year 2050, such that 1 billion people will have some form of osteoarthritis [2]. This is supported by the findings of the Belgian Primary Care Registry study, which found steady increases in prevalence in all age groups between the years 1996 and 2015 [33].

Across the lifecourse, osteoarthritis is more common in women than in men, with an age-standardised prevalence of 8059 per 100,000 (95% confidence interval [CI] 7251.9–8867.9) for women and 5780 per 100,000 (95% CI 5217.8–6341.2) for men [2]. In terms of the effect of age in this global osteoarthritis epidemic, the prevalence of osteoarthritis (as a whole) steadily increases from the age of 40 years until the age of 80 years. At this point, the prevalence continues to increase, although at a less substantial rate [2]. The age distribution for osteoarthritis differs depending on the site, with hip, hand, and 'other' (e.g. shoulder) arthritis increasing constantly from the age of 40 years but with knee osteoarthritis peaking at the age of 80 years and then decreasing thereafter [2]. This distribution was also observed in osteoarthritis cases in a UK primary care database study (in the Clinical Practice Research Datalink) [34]. The fact that this was observed in the entire osteoarthritis population may be due to the high prevalence of knee osteoarthritis in this study (over twice that of hip osteoarthritis and over three times that of hand osteoarthritis), a reduced rate of presentation or diagnosis in this 'oldest old' population, or the competing nature of morbidity.

Indeed, an insurance registry study in Canada, including nearly 500,000 participants, highlighted the high level of comorbidity in those with osteoarthritis, with 29% having hypertension, 20% depression, 19% chronic obstructive pulmonary disease (COPD), 10% diabetes, and 6% congestive heart failure [35].

To summarise, osteoarthritis and osteoporosis are frequent in the oldest old and, if the number of oldest old individuals increases, the prevalence of these diseases of musculoskeletal ageing will increase. The epidemiology of fractures is mapped for age, sex, geography, and time, but the secular trends of osteoarthritis require further research. Further work is also needed to close the treatment gap for osteoporosis in the oldest old.

3 Osteoporosis Interventions

As is the common theme throughout this paper, there is a paucity of data relating to osteoporosis interventions in the oldest old, with the majority of (particularly pivotal) trials neglecting to include this population and a subsequent reliance on post hoc analyses (Table 1). There are multiple causes for this underrepresentation of oldest old adults in clinical trials [36], including ageism (i.e. discrimination towards older subjects) [37].

3.1 Anti-resorptive Therapy

Anti-resorptive medications, which largely inhibit the activity of osteoclasts, are the most commonly prescribed for the treatment of osteoporosis and have been widely studied for efficacy and safety, although less so in the oldest old age group.

The efficacy of alendronate was extensively examined in the Fracture Intervention Trials (FIT), with FIT-1 demonstrating fracture risk reduction (with 22 hip fractures in the placebo group and 11 in the treatment group) in postmenopausal women with a history of radiographic vertebral fracture and DXA-defined low BMD (femoral neck BMD [FN-BMD] < 0.68 g/cm^2) [38] and FIT-2 in postmenopausal women with DXA-defined low FN-BMD alone (<0.68 g/cm^2).

Women aged 55–80 years were enrolled in FIT-I and randomised to placebo or alendronate 5 mg daily for 2 years followed by 10 mg daily for a further 1–2.5 years [38, 39]. A post hoc analysis (of data from FIT-1 and FIT-2 for participants with an osteoporotic level of BMD) of the relative risk (RR) reduction for fracture demonstrated that alendronate reduced the risk of hip fracture by 53% (RR 0.47; 95% CI 0.27–0.81; $p < 0.01$), vertebral fracture by 45% (RR 0.55; 95% CI 0.37–0.83; $p < 0.01$), and distal radial fracture by 31% (RR 0.69; 95% CI 0.50–0.98; $p = 0.04$) [40]. For a composite endpoint of any hip, vertebral, or distal radial fracture, alendronate was associated with a significant risk reduction of 40% (RR 0.60; 95% CI 0.47–0.77; $p < 0.01$) [40]. The absolute risk reduction (ARR) of this composite endpoint was examined in age categories that showed increasing ARR with increasing age, including up to the age of 85 years (ARR 65 per 10,000 person-years for those aged 55 to < 65 years; 161 per 10,000 person-years for those aged 75–85 years), demonstrating the increasing benefit of alendronate versus placebo with age in this group (aged 75–85 years). The oldest old were not included in this study and, to examine the efficacy of alendronate in this population, we must move to evidence generated from real-world data.

A Swedish database of adults who were aged ≥ 80 years and had been referred for falls risk assessment was used as a basis for identifying those who had sustained a prior fracture [41]. Those taking alendronate were identified ($n = 1961$), and propensity score matching was used to identify a control group ($n = 7844$) with incident hip fracture as the primary outcome [41]. The mean age of the analysis group was 84.7 years. Cox proportional hazard models demonstrated that alendronate therapy was associated with a reduced hazard of hip fracture in unadjusted models (hazard ratio [HR] 0.62; 95% CI 0.49–0.79; $p < 0.001$) and in those adjusted for confounders (age, sex, weight, height, and previous medication

Table 1 Characteristics of and efficacy results from post hoc analyses focused on older age groups of pivotal trials for anti-osteoporosis medications

Medication	Comparator	*N*	Age	Fracture site	Effect size
Alendronate [40]	Placebo	3658 (in total)	75–85 years	Any hip, vertebral or distal radial fracture	Hip fracture RR 0.47 (95% CI 0.27–0.81; $p < 0.02$) Vertebral fracture RR 0.55 (95% CI 0.37–0.83; $p < 0.01$) Distal radius RR 0.69 (95% CI 0.50–0.98; $p < 0.04$)
Zoledronate (HORIZON) [48]	Placebo	Zoledronate = 1961; placebo = 1926	≥ 75 years	Clinical fracture, clinical vertebral and non-vertebral fracture	Clinical fracture HR 0.65 (95% CI 0.54–0.78; $p < 0.001$) Clinical vertebral HR 0.34 (95% CI 0.21–0.55; $p < 0.001$) Non-vertebral fracture HR 0.73 (95% CI 0.60–0.90; $p = 0.002$)
Risedronate (HIP) [43]	Placebo	3886 (in ≥ 80-year arm)	≥ 80 years	Hip	Hip fracture RR 0.8 (95% CI 0.6–1.2; $p = 0.35$)
Denosumab (FREEDOM) [53]	Placebo	2471 (≥7 5 years)	≥ 75 years	Hip	Hip fracture RR 0.38 (95% CI 0.18–0.78; $p = 0.07$)
Teriparatide (FPT) [59]	Placebo	244 (≥ 75 years)	≥ 75 years	Vertebral and non-vertebral fracture	Vertebral fracture RR 0.35 ($p < 0.05$) Non-vertebral fracture RR 0.75 ($p = 0.661$)
Abaloparatide (ACTIVE) [62]	Placebo	94 (≥ 80 years)	≥ 80 years	Vertebral and non-vertebral fracture	Vertebral fracture (placebo 2, ABL 0) Non-vertebral fracture (placebo 2, ABL 1) Not statistically significant

ABL abaloparatide, *CI* confidence interval, *HR* hazard ratio, *RR* relative risk

[including glucocorticoids and calcium/vitamin D], secondary osteoporosis, rheumatoid arthritis, alcohol-related diseases, Charlson comorbidity index, time since fracture, previous vertebral fracture, previous hip fracture, previous hip arthroplasty, number of prior fractures, prior falls injury, and prior diagnosis of osteoporosis; HR 0.66; 95% CI 0.51–0.86; $p < 0.01$) [41].

In this group of middle/oldest old adults, alendronate treatment was associated with a reduced risk of mortality (HR 0.88; 95% CI 0.82–0.95) but an increased risk of upper gastrointestinal symptoms (HR 1.58; 95% CI 1.12–2.24) [41], the latter being common to all age groups taking conventional oral bisphosphonates [42].

The Hip Intervention Program (HIP) study was a 3-year, randomised, placebo-controlled trial of risedronate 2.5 mg or 5 mg daily that included an arm of 3886 women aged ≥ 80 years who had at least one clinical risk factor for fracture or very low FN-BMD (*T*-score < – 4 or T-score < – 3 plus a hip-axis length of ≥ 11.1 cm) [43]. Although there was a significant reduction in the risk of hip fracture with risedronate in the other, younger (aged 70–79 years) arm of the study (RR 0.6; 95% CI 0.4–0.9; $p = 0.009$), there was no significant reduction in hip fracture incidence in the ≥ 80-year arm, with an incidence of 4.2% (82 hip fractures) in those taking risedronate ($n = 2573$) and 5.1% (49 hip fractures) in those taking placebo (n = 1313) (RR 0.8; 95% CI 0.6–1.2, $p = 0.35$) [43].

The safety and efficacy of risedronate was examined in an analysis of the oldest old (in this case ≥ 80 years) from pooled trial data including HIP [43], VERT-MN (Vertebral Efficacy with Risedronate Therapy-Multinational) [44], and VERT-NA (VERT-North America) [45]. The population was defined as women aged ≥ 80 years with an FN-BMD T-score of < − 2.5 or at least one prevalent vertebral fracture, with 688 receiving placebo and 704 receiving risedronate 5 mg daily. The vertebral fracture efficacy of risedronate in this population was confirmed across the 3 years of study (HR 0.56; 95% CI 0.39–0.81; $p < 0.001$), but it was particularly striking that the protective effect was observed as early as 12 months after commencing treatment (HR 0.19; 95% CI 0.08–0.40; $p < 0.001$) [46]. The same significant protective effect was not observed for non-vertebral fractures. The authors of this pooled analysis concluded that risedronate was "well tolerated, with a safety profile comparable with that of placebo" [46]. This was even the case for those with baseline active gastrointestinal tract disease and those taking nonsteroidal anti-inflammatory drugs (NSAIDs), proton pump inhibitors (PPIs), or aspirin.

Zoledronate, an intravenous bisphosphonate, was explored in the HORIZON trial [47], and a post hoc analysis was subsequently performed in a population of postmenopausal women aged ≥ 75 years with either a prevalent hip or vertebral fracture or an osteoporotic level of FN-BMD who were randomised to zoledronate 5 mg per year or placebo [48]. Zoledronate significantly protected against any clinical fracture as a whole and hip fracture, non-vertebral fracture, and clinical vertebral fracture individually at both 1 year and 3 years after commencement; the most impressive reduction in risk was for clinical vertebral fracture at 3 years (HR 0.34; 95% CI 0.21–0.55; $p < 0.001$) [48]. The efficacy of zoledronate in reducing fracture risk in a group of individuals with a mean age of ~74 years was demonstrated in the HORIZON recurrent fracture trial, in which zoledronate was given to patients within 90 days of a low-trauma hip fracture (resulting in a 35% risk reduction in clinical fracture: 8.6% in the zoledronate group and 13.9% in the placebo group; $p = 0.001$) [49].

The safety profile reported for those aged ≥ 75 years in the HORIZON trial was similar for zoledronate and placebo, although adverse events within 3 days of infusion were more common in those receiving zoledronate (placebo 25.7% vs zoledronate 41.5%; $p < 0.001$), as were pyrexia (4.0% vs 12.1%, $p < 0.001$), chills (0.6% vs 3.5%, $p < 0.001$), influenza-like illness (2.1% vs 5.2%, $p < 0.001$), myalgia (3.1% vs 8.6%, $p < 0.001$), and bone pain (1.5% vs 4.3%, $p < 0.001$) [48]. Interestingly, an increased risk of atrial fibrillation requiring hospitalisation [50] was observed in younger populations but not in the older age group.

Denosumab, a monoclonal antibody inhibitor of RANK ligand, was examined in the FREEDOM (Fracture REduction Evaluation of Denosumab in Osteoporosis every 6 Months) trial [51], where those aged ≥ 75 years accounted for only 31.6% of the trial population [52]. A post hoc analysis focused on the efficacy of the intervention in high-risk populations, including women aged ≥ 75 years (mean age 78.2 years). The risk reduction for hip fracture in this group was 62% ($p < 0.01$) and comparable to that in the overall trial population [53]. These post hoc analyses demonstrated that adverse effects in the older age group and the study population as a whole were similar [53], although, in clinical practice, it is important to be aware of the increased risk of hypocalcaemia in older adults and those with severe renal impairment (creatinine clearance < 30 mL/min). Calcium and vitamin D levels must be monitored and replaced as appropriate in these groups. The risk of rebound vertebral fractures after discontinuation of denosumab appears to increase with greater duration of treatment [54] and may be at least partly mitigated with one or more doses of zoledronate. A further post hoc analysis of the FREEDOM study compared adults above and below a 75-year age threshold and found similar vertebral fracture protection for those aged ≥ 75 years (RR 0.36; 95% CI 0.25–0.53) as for those aged < 75 years (RR 0.30; 95% CI 0.22–0.41) [55]. Non-vertebral fracture protection was significant for those aged < 75 years (RR 0.78; 95% CI 0.63–0.96) but not in those aged ≥ 75 years (RR 0.84; 95% CI 0.63–1.12) [55].

3.2 Bone-Forming Therapy

Within the panoply of anti-osteoporosis medications, in addition to the anti-resorptive agents already discussed, we have bone-forming, anabolic, bone-remodelling agents that stimulate new bone to form. These consist of recombinant parathyroid hormone (PTH) analogues, including teriparatide and abaloparatide, and the anti-sclerostin monoclonal antibody romosozumab. Network meta-analysis has shown that these bone-forming agents result in greater reduction in the risk of fracture than anti-resorptives [56] and that the fracture-reducing efficacy of bone-forming agents is similar for PTH analogues as for anti-sclerostin agents [57].

The FPT (Fracture Prevention Trial) was a randomised, placebo-controlled trial of teriparatide in postmenopausal women (aged 42–86 years) [58] that demonstrated the BMD gains and fracture protection that could be accrued via teriparatide. The data from the FPT were reviewed in a post hoc analysis to investigate the effect of age, with 75 years as the threshold (two groups: aged < 75 years [$n = 841$] or ≥ 75 years [$n = 244$]) [59]. Although the power of this study was limited by the low number of non-vertebral fractures in the older age group, overall, this study suggested that there was no significant difference in efficacy between the two groups and no difference in terms of safety [59].

Abaloparatide differs in structure to teriparatide, sharing 41% of its structure with PTH 1–34 and 76% with PTH-related protein 1–34 [60], and showed significant efficacy for reducing the risk of vertebral and non-vertebral fractures [61] in postmenopausal women aged > 65 years. A post hoc analysis investigated the efficacy of abaloparatide in the women who were aged ≥ 80 years (abaloparatide, $n = 51$, mean age 81.7 years; placebo, $n = 43$, mean age 81.9 years) [62]. Although significant improvements in BMD were observed in those receiving abaloparatide in this age group (3.6% at the femoral neck and 12.1% at the lumbar spine over 18 months), only numerical benefits and not statistically significant benefits were observed in terms of vertebral (abaloparatide = 0, placebo = 2) and non-vertebral (abaloparatide = 1, placebo = 2) fractures [62]. It should be noted that the power in these analyses may be the limiting factor for the demonstration of a statistically significant effect (e.g., there were only two vertebral fractures and three non-vertebral fractures in this older age sub-group). In terms of safety, there was no clear distinction between the ≥ 80-year age group and the study population as a whole.

Abaloparatide treatment is associated with transient increases in heart rate of mild to moderate severity. These transient increases in heart rate were not associated with an increased number of major adverse cardiovascular events (MACE) or arrhythmias, and no safety signal was identified for cardiovascular events with abaloparatide treatment from the available data, including completed and ongoing clinical studies and approximately 5 years of post-marketing experience data from the USA [63].

A direct comparison of teriparatide against abaloparatide in the real-world data setting of a US claims database suggested that (even after 5 months of treatment) there was a lower risk of hip fracture with abaloparatide, and there was no significant difference in cardiovascular safety profile between these two bone-forming agents, although a higher frequency of cardiovascular events was reported than in the pivotal ACTIVE study [64]. Of note, the incidence of serious cardiovascular events was similar in abaloparatide- and teriparatide-treated patients with a history of stroke or myocardial infarction (MI) within the year before the index date or those with cardiovascular risk factors, representing approximately 75% of patients in this retrospective observational study [63].

One of the pivotal trials of romosozumab, ARCH [65], was a randomised, blinded, alendronate-controlled trial of romosozumab in a population of postmenopausal women ($n = 4093$) treated for 12 months with either romosozumab or alendronate, followed by an open-label period of 12 months of treatment with alendronate in both groups. For the purposes of our review of the oldest old, the mean age of participants was 74 years (in both the alendronate and romosozumab arms), and 52% of participants were aged ≥ 75 years [65]. At 24 months, the romosozumab group had a clear benefit, including a 48% reduction in the risk of vertebral fractures (RR 0.52; 95% CI 0.40–0.66; $p < 0.001$), 27% lower risk of clinical fractures (HR 0.73; 95% CI 0.61–0.88; $p < 0.001$), and 19% reduced risk of non-vertebral fracture (HR 0.81; 95% CI 0.66–0.99; $p = 0.04$). In terms of safety profile, although there was no significant difference in osteonecrosis of the jaw (one episode in each group) and atypical femoral fracture (two events in the romosozumab–alendronate group and four events in the alendronate–alendronate group), more serious cardiovascular events were observed in the romosozumab–alendronate group (2.5%) than in the alendronate–alendronate group (1.9%). There is a rationale behind a potential association between cardiovascular disease and the inhibition of sclerostin [50]; however, it has also been argued that the differential rates in cardiovascular events in the romosozumab group compared with the alendronate group is actually driven by the potential cardioprotective effects of alendronate rather than by the deleterious effects of romosozumab. Indeed, in a smaller randomised placebo-controlled study ($n = 332$) of romosozumab (at doses of 70 mg, 140 mg, and 210 mg) in a postoperative hip fracture population in which over 60% of participants on romosozumab were aged ≥ 75 years, there was no significant difference in MI or fatal adverse events with romosozumab, although the numbers were numerically higher in the romosozumab groups [66].

A meta-analysis of the five trials of romosozumab in postmenopausal females, including ARCH [65], FRAME [67], STRUCTURE [68], McClung et al. [69], and Ishibashi et al. [70], and a single study in men, BRIDGE [71], showed no significant impact of romosozumab on single outcomes, including MI, stroke, cardiovascular death, heart failure, or atrial fibrillation, or on a composite cardiovascular outcome (stroke, atrial fibrillation, heart failure, and coronary artery disease), or 3P-MACE (cardiovascular death, MI, stroke), but did show a significantly adverse effect for romosozumab on 4P-MACE (3P-MACE plus heart failure) [72] (risk ratio 1.39; 95% CI 1.01–1.90). A further Bayesian network meta-analysis of the cardiovascular risk of osteoporosis medications in postmenopausal women alone showed no significant increase in odds of cardiovascular adverse events, including individual and composite outcomes [73]. This network meta-analysis reported a cardioprotective effect of abaloparatide.

A subsequent pharmacovigilance study in the USA and Japan reporting potential romosozumab-related adverse events demonstrated an increased reporting odds ratio of MACE with romosozumab in Japan but not in the USA. This may have been due to the older age and the higher proportion of men in the Japanese population [74].

To conclude, there is evidence of a signal for increased cardiovascular risk with romosozumab from trials, real-world data, and a meta-analysis; however, the association with MACE is only significant if men are included in the meta-analysis. This does not preclude the use of romosozumab (and in men, new data or analyses may become available), which has clear skeletal benefits in reducing fracture risk but does highlight the need to assess cardiovascular risk in patients before commencing therapy. This might take the form of a clinical assessment of cardiovascular risk, perhaps combined with tools used for cardiovascular risk assessment, such as Q-RISK-3 [75]. Comorbidity increases with age and will be substantially raised in the oldest old. For this reason, cardiovascular assessment should be particularly rigorous in women aged > 75 years.

There are no significant cardiovascular safety concerns for teriparatide, and – according to currently available post-marketing experience – this also seems to be the case for abaloparatide. Taking into account new results from an extension of the observational US claims database, which corroborate the previous finding of no significant difference in the safety profiles of abaloparatide and teriparatide [76], it appears reasonable to limit the cardiovascular assessment before prescription of abaloparatide to blood pressure measurements.

3.3 Fracture Liaison Services

So far, we have focused on primary prevention of fractures. Although there are clinically effective and health economically efficient models for screening for osteoporosis [77, 78], a substantial treatment gap remains [79], but secondary prevention still provides an opportunity to reduce the risk of future fractures and may be particularly relevant in the population of the oldest old.

Fracture Liaison Services are models of care that systematically identify those who have sustained a fracture so that they can be appropriately treated and their risk of future fractures reduced. This framework has been shown to be clinically effective and cost effective with reduced mortality [80–82] and is an important facet of the treatment of osteoporosis in the oldest old.

4 Osteoarthritis Interventions

Guidelines for the management of osteoarthritis at the knee, hand, hip, and other joints recommend a stepwise approach to treatment, advocating a multimodal approach using a combination of exercise, dietary optimisation, and weight management, together with pharmacological therapies to benefit patients with the disease [83]. Surgical interventions, including arthroplasty, are associated with significant functional benefits, but the focus of this review is on the pharmacological and (non-surgical) non-pharmacological interventions for osteoarthritis [84].

4.1 Symptomatic Slow-Acting Drugs for Osteoarthritis

Symptomatic Slow-Acting Drugs for Osteoarthritis, including glucosamine and chondroitin, are included in the ESCEO knee osteoarthritis algorithm as a step 1 intervention for symptomatic patients [83]. This is based on evidence from the literature, including a systematic review demonstrating benefits in reduced joint space narrowing and increased cartilage volume (glucosamine standard mean difference [SMD] 0.16; 95% CI 0.04–0.28; chondroitin SMD 0.21; 95% CI 0.10–0.32) and symptomatic benefit in terms of pain (glucosamine SMD − 0.15; 95% CI − 0.25 to − 0.05; chondroitin SMD − 0.06; 95% CI − 0.15 to 0.03), and function (glucosamine SMD − 0.17; 95% CI − 0.28 to − 0.07; chondroitin SMD − 0.15; 95% CI − 0.26 to − 0.03) [85]. The quality of these medications varies, and it is clear that high-quality, prescription-grade formulations have a greater clinical effect than over-the-counter formulations [86–88], and greater effect on radiographic disease [89, 90].

Symptomatic slow-acting drugs for osteoarthritis have a neutral safety profile, as seen in the individual studies already mentioned [91] as well as via meta-analysis [92], and are therefore recommended as long-term therapy in guidelines [83]. Although specific data, including sub-group analysis or de novo studies, are required in the oldest old, the

current data from other age groups suggest that this group of medications is safe to use in the oldest old.

4.2 Analgesic Medications

4.2.1 Paracetamol

Despite the widespread usage of paracetamol, and particularly in the oldest old, who are more likely to have osteoarthritis, there is a distinct paucity of data relating to paracetamol in this population.

In terms of the epidemiology of paracetamol usage, the mean age in osteoarthritis trials is 61–63 years, far below the threshold of the oldest old [93, 94]. Data from the Osteoarthritis Initiative in the USA show that 14% of patients with knee osteoarthritis used paracetamol, whereas a Dutch osteoarthritis survey found that 13.1% of patients had ever taken paracetamol for their condition if they were only taking one medication but that the majority of patients took it in conjunction with another analgesic (e.g., 23% of the study population took NSAIDs and paracetamol) [94]. The 'over-the-counter' availability of paracetamol makes it difficult to track consumption via prescription studies alone. A large study of patients aged ≥ 65 years with chronic pain in Taiwan showed that paracetamol use was highly prevalent in those aged ≥ 85 years, with 76.9% of patients taking the medication [95]. An Australian study of hospital patients with a mean age of 83 years showed that falls and osteoarthritis (both of which are associated with quadriceps weakening) were strongly associated with paracetamol usage and, separately, emphasised the extent of multimorbidity and polypharmacy, which is relevant as we strive to manage osteoarthritis in the oldest old [96].

Efficacy data on paracetamol come via established libraries of evidence, including a Cochrane review [97] that included trials with an age range of 55–70 years and a network meta-analysis of 122 randomised controlled trials of knee osteoarthritis treatments but only one study with a mean age > 70 years [98]. In a further network meta-analysis including 192 trials of hip and knee osteoarthritis medications, only 3% of patients were aged ≥ 70 years [99]; similar proportions of older adults were included in a meta-analysis of osteoarthritis and back pain [100], emphasising once again the paucity of data in the oldest old. In the latter meta-analysis by Machado et al., a significant (though not clinical meaningful) benefit was demonstrated for knee and hip osteoarthritis in terms of pain (weighted mean difference [WMD] − 3.7; 95% CI − 5.5 to − 1.9) and disability (WMD − 2.9; 95% CI − 4.9 to − 0.9) [100].

However, learnings from young age groups can be extrapolated from these data, including an increased risk of abnormal liver function tests with paracetamol usage (WBD 3.8; 95% CI 1.9–7.4) [100] and that the rate of hospitalisation rises with increasing dose of paracetamol [101]. Indeed, the risk of abnormal liver function tests is likely to be higher in the oldest old, given, for example, the higher prevalence of polypharmacy in older age groups. In terms of cardiovascular adverse events, a Spanish registry case–control study demonstrated that paracetamol was not associated with an increased risk of acute MI or stroke [102]. The mean age in this study was 72 years, older than that of the trials in osteoarthritis.

A study investigating paracetamol usage in hospitalised patients with COPD, with a mean age of 85 years, found a time-dependent effect on COPD exacerbation risk at a dose of 4 g per day (the recommended daily maximum dosage), with usage for 7 days associated with a lower risk (HR 0.78; 95% CI 0.67–0.92) and usage for 30 days associated with a higher risk (HR 1.27; 95% CI 1.06–1.52) [103].

The ongoing RETHINK trial holds promise as it is examining the efficacy of analgesics in osteoarthritis, specifically recruiting patients aged ≥ 65 years [104]; however, there remains a distinct lack of efficacy and safety data relating to paracetamol usage in the oldest old, particularly in osteoarthritis. Extrapolation from other disease areas suggests that dose and duration may be important from an efficacy and safety standpoint and that polypharmacy will likely play a substantial role in the pharmacokinetics of paracetamol in the oldest old. There may also be responders and non-responders to this widely used and prescribed medication, which should be an area of future work. In the absence of direct evidence regarding paracetamol in the oldest old, informed clinical practice must centre around current guidance with short-term use only [105, 106].

4.2.2 NSAIDs

Cyclo-oxygenase (COX) has two subtypes. COX-1 is constitutively expressed and plays a key role in the maintenance of renal homeostasis, protection of the gastric mucosa, and regulation of platelet aggregation. COX-2 is induced by cytokines and growth factors as part of a pro-inflammatory response [107]. NSAIDs demonstrate a range of COX selectivity, from those that inhibit both COX-1 and COX-2 to formulations that more selectively target COX-2 [108].

Particular issues need to be considered when using NSAIDs in the oldest old. On one hand, the oldest old patients are more likely to have gastric, cardiovascular, cerebrovascular, and renal comorbidities, which will increase the risk of NSAID-related adverse events [109]. On the other hand, in osteoarthritis populations as a whole, NSAIDs are a useful alternative to opioids for older adults who are known to experience substantial adverse effects (including

constipation, reduced appetite, drowsiness, confusion, and dependence) [109, 110].

A meta-analysis of 68 trials of NSAIDs in hip and knee osteoarthritis demonstrated that, although efficacy (in terms of analgesic effect) may be better with higher dosages, lower doses may still provide some analgesic effect and may be associated with a lower risk of adverse events in an oldest old population [99]. Dose titration is therefore advocated if NSAIDs are used in the oldest old in the absence of relevant comorbidities.

The effect profile of NSAIDs was investigated in a randomised trial of celecoxib, ibuprofen, or naproxen in patients with high cardiovascular risk and either osteoarthritis or rheumatoid arthritis (mean age 63 years, 64% women) [111]. It should be noted that the mean dose of ibuprofen used was > 2 g, which is higher than the usual recommended clinical dosage; however, ibuprofen was associated with higher renal adverse events than celecoxib, with celecoxib having significantly lower gastrointestinal adverse events than ibuprofen (but not significantly lower than naproxen) [111]. There was no significant difference in cardiovascular adverse event profile among the three NSAIDs [111].

Cardiovascular risk with NSAIDs was extensively studied via a meta-analysis including 280 trials of NSAIDs versus placebo and 474 trials of NSAID versus NSAID (encompassing over 200,000 person-years of follow-up). This showed that, compared with placebo, COX-2 inhibitors (coxibs) were associated with an increased risk of MI or coronary heart disease death (RR 1.76; 95% CI 1.31–2.37), major vascular events (RR 1.37; 95% CI 1.14–1.66), death (RR 1.22; 95% CI 1.04–1.44), and particularly heart failure (RR 2.28; 95% CI 1.62–3.20) [112]. Interestingly, compared with non-selective NSAIDS, coxibs were only associated with a greater risk of MI or coronary heart disease death (RR 2.11; 95% CI 1.44–3.09) and major vascular events (RR 1.49; 95% CI 1.16–1.92) when compared with naproxen (and not diclofenac or ibuprofen), emphasising the need to consider cardiovascular risk with coxibs but also with non-selective NSAIDs (perhaps less so with naproxen) [112].

In the same meta-analysis, all NSAIDs were associated with increased upper gastrointestinal complications (coxibs RR 1.81; 95% CI 1.17–2.81; $p = 0.0070$; diclofenac RR 1.89; 95% CI 1.16–3.09; $p = 0.0106$; ibuprofen RR 3.97; 95% CI 2.22–7.10; $p < 0.0001$; and naproxen RR 4.22; 95% CI 2.71–6.56; $p < 0.0001$) [112].

The absolute impact of adverse events in coxibs was summarised in a meta-analysis of 36 osteoarthritis studies, which reported a risk difference with coxibs (vs placebo) to be 5 more per 1000 patients for upper gastrointestinal adverse events, 9 more per 1000 patients for abdominal pain, 12 more per 1000 patients for hypertension, and 7 more per 1000 patients for heart failure and oedema.

As mentioned, the mean age in osteoarthritis trial populations is in the early 60-year bracket, and it is likely that the rate of adverse events will rise beyond those quoted above in the oldest old. Real-world data suggest an increased risk of acute kidney injury, particularly when treating with non-selective NSAIDs [113].

PPIs attenuate the upper gastrointestinal adverse effects of non-selective NSAIDs; however, there is evidence to suggest that PPIs do not provide protection from, and may even exacerbate, lower gastrointestinal adverse effects, perhaps via alteration of the microbiome [114, 115].

The above should inform a clinical approach to treating osteoarthritis in the oldest old via both non-selective NSAIDs and coxibs. Cardiovascular, gastrointestinal, haemorrhagic, and renal risk should be carefully assessed before commencing NSAID therapy. Blood pressure should be monitored and gastroprotection provided (bearing in mind the risk to the lower gastrointestinal tract). Diclofenac and rofecoxib should be avoided because of their high cardiovascular risk. Renal toxicity may be lower with celecoxib than with non-selective NSAIDs. In general, NSAIDs should be used at the lowest dose for the shortest duration.

5 Diet

The potential impact of diet on both osteoporosis and osteoarthritis has been extensively considered, and the impact of quality of diet throughout the lifecourse may come to bear in the oldest old. Nutritional research is limited by issues with randomisation of diet, so robust trials are limited to dietary supplementation.

Nevertheless, the International Osteoporosis Foundation [116] has published extensive guidelines for calcium, vitamin D, and protein intake within a balanced diet to support bone health. These contain specific recommendations for older (including the oldest old) adults, including calcium intake recommendations of 1200 mg daily for those aged ≥ 70 years and vitamin D intake of 800 IU daily for those aged ≥ 71 years, and protein intake ≥ 0.8 g/kg body weight/day (above the recommended daily allowance, and usually in the range of 1.0–1.2 g/kg body weight/day) may be recommended for the oldest old) [116].

Overall, inferences on the effect of nutrition on osteoarthritis and osteoporosis in the oldest old must be drawn from studies in younger cohorts [117].

5.1 Osteoporosis

5.1.1 Macronutrients

Omega-3 fatty acids modulate the activity of osteoclasts and osteoblasts, dampen inflammatory processes, and regulate

calcium metabolism, working in consort to potentially benefit bone health. However, evidence regarding prevention is limited, and a systematic review of the literature demonstrated no effect of n-3 fatty acids on bone health [118, 119].

Data around carbohydrates are sparse, but a single study in postmenopausal women showed that diets with a higher glycaemic index increased the risk of osteopenia and osteoporosis, with higher carbohydrate quality index leading to a reduced risk of low BMD [120].

More data are available about protein intake (although not in the oldest old). A meta-analysis of 12 cohort studies and randomised controlled trials have demonstrated a positive trend between higher protein intakes and higher femoral neck and total hip BMD [121]. A meta-analysis of four cohort studies showed that higher protein intakes were associated with a significantly lower risk of hip fractures (pooled HR 0.89; 95% CI 0.84–0.94) [121]. This is supported by other meta-analyses [122, 123] and supports the assertion that a higher protein intake, of 1.2–1.5 g/kg body weight/day should be considered for the oldest old [124].

5.1.2 Micronutrients

In terms of micronutrients, excess phosphorus should be avoided, particularly in those with low-calcium diets, and magnesium levels should be replete, derived ideally via diet rather than supplementation [125, 126].

Vitamin intake should be adequate, including B_{12} vitamins [127] and vitamin C [128], and there is moderate evidence of a similar effect for vitamin E [129]. The data regarding vitamin K are more mixed, with no clear effect [130, 131].

Like bisphosphonates, phytates are analogues of pyrophosphate, and a diet rich in phytates (via legumes, cereals, nuts) is associated with better BMD [132].

5.1.3 Foods

When it comes to foods and dietary patterns, there are theoretical benefits of dairy products on bone via calcium intake, but meta-analyses of longitudinal studies are largely null [133, 134]. This should not dampen recommendations around dairy intake for protein and calcium intake [135], or indeed fermented dairy products [136, 137] and the potential role of the gut microbiome [138]. Soy, mostly supplemented to provide isoflavones, shows some relationship with BMD [139], and intake of at least 5 cups per day of green tea has been associated with small improvements in BMD and reduced fracture risk [140].

5.2 Osteoarthritis

Most nutritional studies in osteoarthritis are, quite correctly, centred on obesity. However, systematic reviews have shown a reduced prevalence of osteoarthritis and improved quality of life in those taking a Mediterranean diet and reduced progression of symptoms with a prudent diet [141]. Although some studies have examined the effect of alternative, supplemental therapies, many of these only show benefit in symptoms but not in disease modification [142]. The gut microbiota is another area of interest and may be a future target for interventions [138, 143].

6 Exercise

Musculoskeletal ageing, including in the oldest old, is associated with mitochondrial dysfunction, hormonal function, neuromuscular impairment, reduced protein turnover, reduced cardiorespiratory function, impaired myogenic capacity, and an increasingly pro-inflammatory cytokine milieu [144].

The World Health Organization provided guidelines on physical activity in 2020 [145], with a general rule being 'start low and go slow' but ultimately aiming to exercise more than 300 min per week for everyone who can, and older adults should aim to perform multicomponent activities for strength and balance on at least 3 days per week.

There is a graded relationship between average daily energy expenditure and benefits for osteoarthritis. Evidence from the Osteoarthritis Initiative suggests that 150 min of moderate–vigorous physical activity (MVPA) per week reduces functional decline by 32% [146], but—even at lower levels of physical activity (55 min of MVPA/week)—patients with osteoarthritis can maintain disability-free status at 4 years [147]. Even if there were no bout of MVPA during the week but physical activity levels increase, then disability can be reduced [148]. Indeed, breaking the habit of sedentary behaviour may be a good aim and target for physical intervention in older adults [149].

Physical activity can take many forms, including household chores, and those participating in < 1 h of household activities (including chores) have a higher risk of hip fracture (HR 1.85; 95% CI 1.01–3.38) than those participating in > 6 h of household activity [150].

Structured exercise centres around resistance training, functional training, balance training, impact training, and aquatic therapy. Exercise prescription for older adults should focus on increasing the speed of movement to counteract the loss of fast-twitch muscle fibres, diversifying load direction, and applying loads rapidly to reduce

falls risk and aiming to progressively overload to improve performance. The muscle groups targeted may be different for osteoarthritis of the knee, where the focus may be on quadriceps muscle strength, compared with for osteoporosis, where the focus may be directed to the specific areas most vulnerable to fracture. For example, targeting the lower quarter for those more vulnerable to hip fracture or targeting the core musculature and back for those more vulnerable to vertebral fracture. All patients with osteoporosis are advised to perform exercises to improve balance and minimise falls.

Systematic reviews highlight the importance of potentially focusing on single intervention resistance training in the oldest old to improve strength if compliance is an issue with multicomponent approaches [151].

When considering strengthening approaches, to optimise training, exercise should be supervised by a physical therapist, the minimum effort should be 40–60% for one repetition, and the task should feel moderately hard to perform. The number of repetitions can be a set number (e.g., 10–15) of 'good form' or according to the threshold whereby the individual has no more than three 'repetitions in reserve' [152]. Three or more sessions should be performed per week, with 24–48 h rest between sessions. This can lead to a 30% reduction in the pain from knee osteoarthritis.

High-intensity resistance training, progressing gradually over 12 weeks from education to explosive movements, has been shown to benefit older men with osteosarcopenia and has been associated with improvements in lumbar spine BMD (measured via quantitative computed tomography) and skeletal muscle mass index [153]. The Otago Falls Program and GLA:D® [154] international programme are exemplars of programmes for improving falls risk and symptoms from osteoarthritis, respectively.

Exercise parameters that should be the subject of future work in the oldest old include muscle power (including ballistic exercises), adherence to therapy, and adaption.

7 Health Economics

Analysis of health economics is vital in the current healthcare environment with rising demands and budgetary constraints. Health technology assessment is a broad scientific field that encompasses a multi-disciplinary process incorporating various dimensions of value, including effectiveness of an intervention, safety, costs, ethical-social-cultural factors, legal framework, and the environment and sustainability [155, 156]. An economic evaluation typically investigates the (societal) costs against the number of quality-adjusted life-years (QALYs, where 1 QALY corresponds to 1 year in perfect health). When the intervention is associated with more QALYs for lower cost, the intervention is said to be dominant. For interventions associated with more QALYs and more costs, the incremental cost-effectiveness ratio (ICER) is investigated. The lower the ICER, the more cost effective the intervention.

7.1 Osteoporosis

The cost effectiveness of anti-osteoporosis medications has been analysed in multiple studies [80, 157–160], which have concluded that these interventions are generally cost effective in men and women with low bone mass and/or fractures over the age of 60 years.

The increased incidence and high costs resulting from fractures in the oldest old means that, in terms of acute management and long-term care requirements, the cost effectiveness of these medications rises with age [161] and is often dominant in the oldest old (as the cost of the treatment is less than the cost of fractures prevented). The ICER reduces with increasing age because of the higher fracture incidence with increasing age.

7.2 Osteoarthritis

Several studies have investigated the cost effectiveness of interventions for osteoarthritis [162–165]. The cost effectiveness of these interventions (including pharmacological and non-pharmacological interventions) is heterogeneous, although most studies found interventions to be cost effective (for specific ICER thresholds). Very few studies included the oldest old. Mazzei et al. [164] included individuals aged > 50 years and found that most osteoarthritis interventions were cost effective or dominant, and Kunkel et al. [166] demonstrated the cost effectiveness of total hip replacement as a surgical intervention for hip osteoarthritis in patients aged ≥ 80 years.

In summary, treatment strategies for osteoarthritis and osteoporosis are cost effective in the oldest old, although relatively few analyses have incorporated individuals aged ≥ 80 years.

8 Conclusions

Despite osteoarthritis and osteoporosis being highly prevalent in the oldest old, data to inform clinical practice in this population are remarkably sparse.

This evidence gap is particularly wide in trials in osteoarthritis, which generally have a mean age in the early 60s. Real-world data on pharmaceutical interventions in osteoarthritis are hampered by the inability to readily record the

intake of over-the-counter medicines (such as paracetamol and NSAIDs). In osteoporosis, the evidence for older age groups comes largely from post hoc analyses of pivotal trials but very rarely include the oldest old. It should also be emphasised that, although the relative fracture risk reduction may be similar across age groups, the absolute fracture risk reduction is greater in the oldest old.

Medications for osteoarthritis and osteoporosis should be prescribed after a thorough assessment of comorbidity and polypharmacy in each individual patient. It should also be considered that chronological age is a single measure of ageing, and substantial biological ageing can occur at younger ages, and the same careful approach should be taken to these 'accelerated ageing' patients.

We finish with a call to fight ageism and for further research (clinical, epidemiological, and health economic) focusing on interventions for osteoporosis and osteoarthritis in the oldest old to counteract the projected increases in prevalence that will arrive with the ageing epidemic.

Acknowledgements This work was supported by the Distinguished Scientist Fellowship Program (DSFP) of the King Saud University, Riyadh, Kingdom of Saudi Arabia.

Declarations

Funding The ESCEO working group was funded by the ESCEO. The ESCEO receives unrestricted educational grants to support its educational and scientific activities from non-governmental organisations, not-for-profit organisations, non-commercial, or corporate partners. The choice of topics, participants, content, and agenda of the working groups as well as the writing, editing, submission, and reviewing of the manuscript are the sole responsibility of the ESCEO, without any influence from third parties.

Conflict of Interest NA-D, MA, CB, ABvB, NB, EC, MC, AC, PGC, EC, PD'A, BD-H, J-MK, SM, RM, EM, ODM, DP, MCPY, RPR and JAK, and have no competing interests to declare with respect to this manuscript. NF has received honoraria and speaker fees from Viatris and UCB. RRi has received fees for advisory board participation or lectures from Abiogen, Effryx, and Theramex. NCH has received personal fees, consultancy, lecture fees and/or honoraria from Alliance for Better Bone Health, AMGEN, MSD, Eli Lilly, UCB, Kyowa Kirin, Servier, Shire, Consilient Healthcare, Theramex and Internis Pharma. OB has received consulting or lecture fees from Amgen, Aptissen, Biophytis, IBSA, Mylan, Novartis, Nutricia, Orifarm, Sanofi, UCB, and Viatris. BC has received personal fees, consultancy fees, lecture fees, and honoraria from Alexion, Amgen, Expanscience, Kyowa-Kirin, MSD, Novartis,Theramex, UCB, and Viatris. AC-J has received honoraria for teaching activities from Abbott Nutrition, Fresenius Kabi, Nestlé Health Care, and Nutricia Danone. EMD has received consultancy honoraria and speaker fees from UCB, Pfizer, Viatris, and Lilly. MH has received research grants (paid to institution) from Radius Health and Angelini Pharma and lecture fees from IBSA (paid to institution) and Mylan Pharmaceuticals and was grant advisor for Pfizer (paid to institution). YR has received support from CHU Toulouse, University Paul Sabatier, and INSERM CERPOP1295 (employee); is a shareholder of SARQOL SPRL, a spin-off of the University of Liege; and has received consultancy fees from Longeveron and Biophytis and honoraria for lectures from Pfizer. NV has received personal fees from MYLAN, FIDIA, IBSA, Viatris, and Nestlè. AL is a member of the Scientific Advice Working Party at the European Medicines Agency and has no conflicting interests to declare. EB-I is a member of the CHMP, SAWP, CNSWP, PCWP, and ETF (European Medicines Agency) and has no conflicting interests to declare. FC has no competing interests with respect to this manuscript. CT is a member of the CHMP, PRAC, and MWP (European Medicines Agency) and has no conflicting interests to declare. MMR is a member of the SAWP and CNSWP (European Medicines Agency) and has no conflicting interests to declare. The views expressed in this article are the personal views of the authors and may not be understood or quoted as being made on behalf of or reflecting the position of any employing organisations or the regulatory agencies by which the authors are employed or affiliated, the European Medicines Agency (EMA), or one of its committees or working parties. CC has received personal fees, consultancy, lecture fees and/or honoraria from ABBH, Amgen, Eli Lilly, GSK, Medtronic, Merck, Novartis, Pfizer, Roche, Servier and Takeda. JYR has received consulting fees or paid advisory boards for IBSA-Genevrier, Mylan, Radius Health, Pierre Fabre, Faes Pharma, Rejuvenate Biomed, Samumed, Teva, Theramex, Pfizer, Mithra Pharmaceuticals, lecture fees when speaking at the invitation of the sponsor for IBSA-Genevrier, Mylan, Cniel, Dairy Research Council (DRC), Nutricia, Danone, Agnovos and grant support from IBSA-Genevrier, Mylan, Cniel, Radius Health, TRB.

Availability of Data and material Not applicable.

Ethics Approval This narrative article contains no original data, so issues of ethics, informed consent, and patient confidentiality do not apply.

Consent to Participate Not applicable.

Consent for Publication Not applicable.

Code Availability Not applicable.

Author Contributions All authors contributed to the discussion of the subject matter. NF, AL, RR, JYR, and NCH wrote the draft manuscript. All authors reviewed and commented on the manuscript.

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