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Osteoporosis (A Lau, Section Editor)

Postmenopausal Osteoporosis Treatment Update

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Abstract

Purpose of review To summarize existing evidence on the treatment of postmenopausal osteoporosis.
Recent findings Despite increased interest in new targets for osteoporosis therapy, the mainstay of treatment remains to be bisphosphonates, denosumab, and teriparatide. Abaloparatide is a new parathyroid hormone-related peptide analog that has similar efficacy as teriparatide, but with monthly doses and a lower risk of hypercalcemia. This medication is approved in the USA for severe osteoporosis, but approval is pending in other countries. Romosozumab is a monoclonal antibody directed against sclerostin that has superior fracture protection compared with alendronate, but it may increase the risk of cardiovascular events based on the recent ARCH trial.
Summary A combination of falls prevention, exercise, and adequate intake of calcium and vitamin D is recommended for prevention and treatment of osteoporosis. Pharmacologic therapy should be added to patients at high risk of fractures.

Introduction

Osteoporosis is a bone disease characterized by demineralization and architectural disruption leading to increased risk of fractures. The prevalence of osteoporosis rises with age, with a prevalence of 16–38% in postmenopausal women of industrialized countries [1]. Osteoporosis is diagnosed by either having a fragility fracture or a bone mineral density (BMD) T score of ≤ –2.5 at the femoral neck [2, 3•]. A fragility fracture occurs during a low impact event where a fracture would not be expected (e.g., a fall from standing height).

BMD is measured by dual-energy X-ray absorptiometry (DXA) scan at various points in the body, and the T score is a measure of standard deviation from the population mean using young woman aged 20–29 years as reference [2]. Femoral neck T score is predictive of fractures in both women and men [4]. Although low BMD is predictive of fractures, it is inadequately sensitive (22.4% using a T score cutoff ≤ 2.6), meaning that most people with osteoporotic fracture T scores do not reach diagnostic threshold [5]. Other fracture assessment tools combine BMD with clinical risk factors to further refine the probability of fracture [6]. The most commonly used tool is FRAX (https://www.sheffield.ac.uk/FRAX/). However, FRAX does not include additional risk factors for the frail elderly in long-term care (LTC), such as dementia and falls. The Fracture Risk Scale has been developed using the Resident Assessment Instrument Minimum Data Set tool for LTC patients [7•].

The primary consequence of osteoporosis is a fracture, which can have significant consequences in terms of functional capacity, ability to live independently, quality of life, and survival [8–11]. Vertebral fractures are associated with recurrent fractures and increased mortality [12]. Hip fractures are more devastating, leading to institutionalization, disability, and ~30% mortality at 1 year [13, 14]. Falls are the most common cause of osteoporotic fractures, particularly hip fractures [15]. Therefore, an integral part of osteoporosis treatment is falls prevention. A recent systematic review and network meta-analysis identified several interventions that effectively reduce falls [16].

The management of osteoporosis involves both non-pharmacologic and pharmacologic interventions. Risk factors for fractures such as falls, glucocorticoid use, smoking, alcohol use, diabetes, thyroid disease, and hypogonadism should be managed. Medications that increase the risk of falls [17] and bone loss [18] should be dose-adjusted or avoided if appropriate (Table 1). Non-pharmacologic management of osteoporosis begins with exercise and vitamin D and calcium repletion. Key pharmacologic interventions include bisphosphonates, denosumab, teriparatide, and selective estrogen receptor modulators (SERM).

Most of the studies of osteoporosis therapy are in postmenopausal women because the risk of fractures is higher in this group compared with older men [20]. This evidence summary is for postmenopausal osteoporosis. Recommendations for male osteoporosis [21], glucocorticoid-induced osteoporosis [22•], and osteoporosis in LTC [23••] are available elsewhere.

Non-pharmacologic therapy

Non-pharmacologic therapy of osteoporosis includes exercise, smoking cessation, and vitamin D and calcium supplementation. These recommendations should be considered for all older adults for prevention of osteoporosis.

Exercise and falls prevention

There are no randomized trials of exercise powered for fracture reduction as primary outcome [24]. The evidence is further limited by the quality of existing studies, small sample size, and heterogeneity of benefit across studies [24–26]. However, there is high quality evidence that exercise programs that prevent falls [27, 28], which is the cause for nearly all hip fractures [15]. While available evidence is limited, most experts agree that a mix of aerobic, resistance, and balance exercises are recommended for patients with osteoporosis [29]. In frail older adults in LTC, exercise should be combined with a multifactorial falls reduction strategy because exercise alone may transiently increase the risk of falls [23••].

Vitamin D and calcium

Sufficient calcium and vitamin D intake is required for bone health. While low calcium intake and vitamin D deficiency are associated with increased fracture

Table 1. Medications associated with increased risk of falls and bone loss [17–19]

Medication	Associated with falls	Associated with bone loss
Glucocorticoid		✓
Heparin		✓
Proton pump inhibitors		✓
Calcineurin inhibitor		✓
Gonadotropin-releasing hormone agonists		✓
Aromatase inhibitors		✓
Medroxyprogesterone		✓
Excess thyroid hormone		✓
Thiazolidinediones		✓
SGLT-2 inhibitors	✓	✓
Any drug that causes hypoglycemia	✓	
Alcohol	✓	✓
Antiepileptics	✓	✓
Serotonin selective reuptake inhibitors	✓	✓
Any antidepressant	✓	
Antipsychotics	✓	
Benzodiazepines	✓	
Any sedative/hypnotic	✓	
Opioids	✓	
Anti-hypertensives	✓	
Diuretics	✓	

risk [30, 31], there continues to be controversy about the efficacy of these two supplements for fracture prevention. The most recent controversy comes from a 2017 update of existing systematic reviews of calcium and vitamin D supplementation trials in community-dwelling elderly patients [32]. Not only did this meta-analysis not find benefit but also it actually found a trend towards increased fracture risk with supplementation. This is in contrast to several other systematic reviews that showed a benefit of calcium and vitamin D [33–35], particularly in institutionalized patients who tend to be more vitamin D deficient than community-living elders [36]. The reason for this is likely due to (1) pooling of studies with subtherapeutic doses of vitamin D (< 800 IU/day) [33], (2) pooling of studies with intermittent high doses of vitamin D (≥ 100,000 IU per dose), and (3) the addition of a large 2017 trial of monthly high-dose (100,000 IU) vitamin D2 [37]. Intermittent high doses of vitamin D paradoxically increases falls and fractures based on evidence from several large RCTs [38–40]. The reason may be a "protective" enzymatic response that decreases conversion of cholecalciferol to active 1,25-dihydroxyvitamin D [41]. Therefore, caution should be taken when interpreting systematic reviews of vitamin D and calcium. Note that all clinical trials of osteoporosis medications require daily

vitamin D and calcium supplementation, indicating a commonly agreed prerequisite for osteoporosis treatment. We recommend following national and international osteoporosis recommendations when deciding on treatment [23••, 42••, 43••, 44••].

To summarize evidence on calcium and vitamin D:

- Daily dosing of vitamin D3 (cholecalciferol) supplementation of 800 IU or greater is recommended for prevention of osteoporotic fractures [33]. This is particularly important in those with vitamin D deficiency (25-hydroxyvitamin D level < 50 nmol/L or < 20 ng/ml). Risk factors for vitamin D deficiency include indoor work, institutionalization, higher latitude, and older age [45]. The optimal vitamin D level is 75 nmol/L (30 ng/ml) [46, 47]. There is no benefit in replacing vitamin D if levels are replete (> 75 nmol/L). Daily dose of vitamin D3 below 800 IU is not sufficient to reach vitamin D serum targets [48] and does not prevent fractures [33]. Serum 25-hydroxyvitamin D level > 125 nmol/L (> 50 ng/ml) may lead to adverse effects according to the Institute of Medicine dietary reference [49]. The safe upper limit of vitamin D3 is 4000 IU per day.
- The recommended total daily intake (food and supplements) of elemental calcium is 1200 mg for prevention of fractures [34, 50]. Calcium carbonate (40% elemental calcium) should be taken with meals because it requires an acidic environment for absorption. Calcium citrate (21% elemental calcium) is less dependent on acidity, and can be taken without food or used concomitantly with acid-suppression medications. Calcium should be taken through the diet (e.g., dairy products, canned sardines, almonds, and tofu) with supplement as necessary to reach 1200 mg daily.
- There is controversy about calcium supplements increasing the risk of cardiac disease when studies used self-reported myocardial infarctions as the outcome [51]. Calcium supplements can cause abdominal pain, which can be mistaken for chest pain. A later systematic review using confirmed myocardial infarctions did not find an association with calcium use [52]. Furthermore, calcium supplementation does not increase coronary artery calcification [53], which is the theorized mechanism for cardiac risk. Unlike calcium supplementation, dietary calcium has not been linked to increased cardiovascular events.
- Adherence to calcium and vitamin D supplementation is important for bone protection. In the Women's Health Initiative (WHI) trial, adherence to supplementation was linked to significant fracture reduction [54]. Trials in institutionalized settings where adherence is high results in lower fracture risk [36], while trials in community-dwelling individuals tend to have low adherence (~ 50%) and low efficacy [55]. Real world adherence may be even lower (20–30%) [56]. Therefore, encouraging adherence is important.

Pharmacologic therapy

Pharmacologic therapy for postmenopausal osteoporosis should be considered for individuals at high risk of fractures. We will review the evidence for bisphosphonates, denosumab, teriparatide, SERM, and estrogen. We will not

review the evidence for strontium ranelate and calcitonin as they are not recommended for osteoporosis therapy due to safety concerns and relatively low efficacy [55].

Mechanism of osteoporosis drugs

There are two main types of osteoporosis drugs: anti-resorptive agents and anabolic agents [57]. The primary mechanism for postmenopausal osteoporosis is an increase in osteoclast activity [58], shifting the balance of bone metabolism to resorption. Anti-resorptive agents work by inhibiting osteoclast-mediated bone resorption, thereby slowing bone loss. Bisphosphonates, denosumab, SERMs, and estrogen are all anti-resorptive agents. Bisphosphonates attach to hydroxyapatite minerals in bones, and are taken into osteoclast during bone resorption [57]. In response, osteoclasts undergo apoptosis, thus slowing bone resorption. Denosumab is a monoclonal antibody that inhibits the receptor activator of nuclear factor kappa-B ligand (RANKL) [59], which is required for differentiation and maturation of osteoclasts. Estrogen deficiency in menopause causes increased RANKL expression on bone cells, which leads to bone resorption [60]. Estrogen replacement reverses this effect. SERMs act as estrogen agonists in the bone and liver but not in other organs [57], mimicking the effect of estrogen in slowing bone loss.

Teriparatide is a recombinant peptide containing the first 34 amino acids of human parathyroid hormone (PTH). Persistent elevation of PTH in hyperparathyroidism leads to bone resorption, by pathologically releasing excess calcium to the blood. In contrast, intermittent pulses of PTH reverse this effect and can even shift the balance to bone formation [61]. Teriparatide is an anabolic bone agent. Given as a daily injection, teriparatide provides intermittent pulses of PTH stimulation, leading to bone formation.

Indications for pharmacologic therapy

Major guidelines recommend initiation of pharmacologic therapy for osteoporosis [42••, 43••, 44••]. The decision should be guided by clinical risk factors, a history of fragility fractures and BMD. Using the FRAX tool, patients should be stratified into high (> 20%), moderate (10–20%), and low risk (< 10%) of major osteoporotic fractures in the next 10 years. Treatment is recommended for those in the high risk category. Moderate risk patients should be assessed individually and the decision to start on therapy is a case by case decision. Patient preferences should always be incorporated for shared decision-making.

Choice of drug

In general, bisphosphonates are the first choice of therapy for most individuals without chronic kidney disease (GFR > 30 ml/min). For those with contraindication or intolerance to bisphosphonates, swallowing, or renal impairment, denosumab is a good alternative. Teriparatide is reserved for individuals with severe osteoporosis and may improve quality of life in those with painful acute vertebral fractures. SERMs can be considered in those with a concomitant need to prevent estrogen-related malignancies, but this class of medications is less effective and increases venous thromboembolism risk. Estrogen, though effective for fracture prevention, should not be used solely for osteoporosis given the well-established risk of cardiac disease, venous thromboembolism, and cancer.

Interpreting the efficacy of osteoporosis drugs

When interpreting the efficacy of osteoporosis drugs, it is important to recognize the following:

- Fracture prevention is the most clinically important outcome for osteoporosis treatment. Although improvements in BMD are a useful surrogate measure, evidence of fracture reduction is required for translation into clinical practice.
- Hip fractures are less common than other fracture types, but they are the most consequential, leading to significant disability, loss of independence and mortality [9]. We recommend choosing an osteoporosis medication with evidence for hip fracture reduction (risedronate, alendronate, zoledronate, and denosumab). Similarly, vertebral fractures are associated with increased mortality [12], so medications should also have proven efficacy in preventing vertebral fractures.

Bisphosphonate

Bisphosphonates are first-line therapy for most patients. Alendronate [62, 63], risedronate [64–67], and zoledronate [68, 69] are the most commonly used bisphosphonates and they all have efficacy in preventing hip and vertebral fractures [70]. Alendronate and risedronate are oral medications taken weekly [71, 72]. Risedronate is also available in once monthly dosing [73]. Zoledronate is an intravenous (IV) medication given once yearly. The HORIZON-RFT trial showed that zoledronate 5 mg IV yearly first dose given within 90 days of a hip fracture resulted in a mortality benefit (hazard ratio 0.72, 95% CI 0.56–0.93) [69]. Ibandronate is another bisphosphonate with evidence for vertebral and non-vertebral fracture reduction, but it does not have efficacy for hip fracture reduction [70]. Clodronate [74], pamidronate, and etidronate are less commonly used for osteoporosis, due to limited availability in certain parts of the world and less evidence for fracture reduction in osteoporosis.

Bisphosphonates are renally excreted, so they are contraindicated in renal impairment (GFR < 30 ml/min) [75•]. Oral bisphosphonates are associated with pill esophagitis [73], so patients have to sit upright for 30 minutes after ingestion. Oral bisphosphonates are also poorly absorbed (bioavailability < 1%) and need to be taken at least 30 minutes before the first meal of the day [76]. Zoledronate is associated with various infusion reactions including fever, myalgia, influenza-like illness, headache, and arthralgia [68]. Zoledronate is also associated with an increased risk of serious atrial fibrillation in the HORIZON-PFT trial [68], but postmarketing surveillance did not confirm this risk [77]. There is a small risk of hypocalcemia with zoledronate use [75], so repletion of calcium and vitamin D is important prior to use.

There are concerns about the long-term safety of bisphosphonates, including the risk of osteonecrosis of the jaw (ONJ) and atypical femur fractures (AFF). ONJ is characterized by exposed bone in the jaw that does not heal by 8 weeks [73]. The risk of ONJ in osteoporosis is low (1.04 per 100,000 patient-years), but the risk in malignancy is much higher (442 per 100,000 patient-years) [78]. In contrast, the risk of a major osteoporotic fracture in women with low, medium, and high risk is 650 in 100,000, 1600 in 100,000, and 3100 in 100,000 patient-years, respectively [79]. AFF is a transverse fracture in the subtrochanter or femur shaft that is not associated with trauma [80]. The risk of

AFF increases with duration of bisphosphonate use, from 1.78 in 100,000 patient-years with 1 year of exposure to 113.1 in 100,000 patient-years with 8 years of exposure [81]. Patients in low-to-moderate risk categories can consider stopping bisphosphonates after 3–5 years of use (drug holiday), with periodic reassessment of risk. Those who are at high risk of fractures should not stop treatment because the risk of fracture is 30 times higher, even after 8 years of exposure. The benefits greatly outweigh potential adverse effects. The risk of AFF is also 6-fold higher in Asian women for reasons that are not fully understood [82].

Denosumab

Denosumab is given as a subcutaneous injection every 6 months. The FREEDOM trial ($n = 7868$) demonstrated its efficacy in vertebral fracture (RR 0.32, 95% CI 0.26–0.41; $p = 0.001$) and hip fracture (RR 0.60, 95% CI 0.37–0.97; $p = 0.05$) reduction for treatment of postmenopausal osteoporosis [83]. The FREEDOM extension trial ($n = 4550$) allowed crossover of the participants receiving placebo to the active drug, and followed all participants for 10 years. Denosumab maintained efficacy in fracture reduction (vertebral fracture 0.90–1.86% yearly incidence, hip fracture 0.07–0.42% yearly incidence) [84]. Two cases of AFF and 13 cases of ONJ were reported in the cohort. The risk of infection, cellulitis, malignancy, and hypocalcemia in the extension cohort was similar to the original placebo group [84]. There are reports of rapid bone loss after discontinuation of denosumab, with gains in BMD reversed to baseline by 12 months, therefore suggesting high risk patients should remain on denosumab [85, 86]. Patients at high risk of fractures should continue denosumab. Patients at lower risk considering discontinuation should be closely monitored to track bone loss.

Although denosumab can be used in renal failure, its use in severe renal impairment and dialysis is associated with increased risk of hypocalcemia despite adequate repletion of calcium and vitamin D (15%) [87].

Teriparatide and PTH analogs

Teriparatide is given as a daily subcutaneous injection for at most 2 years treatment duration. The Fracture Prevention Trial randomized women with postmenopausal osteoporosis and a prior vertebral fracture to teriparatide 20 mcg, 40 cg, and placebo daily for 21 months [88]. There was a significant reduction in vertebral (RR 0.35, 95% CI 0.22–0.55) and non-vertebral fractures (RR 0.47, 95% CI 0.25–0.88). The trial was not powered for hip fractures. There was no difference between 20 and 40 mcg doses, so the lower dose was approved for clinical use. Teriparatide is typically reserved for severe osteoporosis (T-score < 3.5 without fracture or T-score < 2.5 with fragility fracture) or failure of other therapies [89, 90]. Some experts use teriparatide for treatment of AFF, but evidence for improving fracture healing is inconsistent [91]. Contraindications to teriparatide are renal failure (GFR < 30 ml/min) and conditions that increase bone turnover, including hypercalcemia, hyperparathyroidism, Paget's disease of the bone, increased alkaline phosphatase, and other bone malignancies [92]. Early animal studies raised concerns of osteosarcoma risk with long-term use of teriparatide, limiting trial evidence to 2 years of treatment duration, after which the patient should switch to an anti-resorptive

agent. Postmarketing surveillance did not find an association with osteosarcoma [93].

Teriparatide has the added benefit of reducing new or worsening back pain in those with vertebral fracture. A meta-analysis of randomized controlled trials showed a lower risk of any back pain with teriparatide compared with placebo or bisphosphonate (RR 0.66, 95% CI 0.55–0.80) [94]. However, teriparatide does not appear to have any benefit in treatment of back pain caused by vertebral fractures compared with risedronate [95].

Combination and sequential therapy of teriparatide with anti-resorptive agents have been investigated. Combination therapy of teriparatide with alendronate has no synergistic effect on BMD improvement [96, 97]. Although combination teriparatide with denosumab increased BMD, there is no data on fracture outcomes [98]. Combination therapy is generally not recommended. Sequential therapy with teriparatide after bisphosphonates [99] or raloxifene [100] leads to improvements in BMD. As mentioned above, sequential anti-resorptive therapy after teriparatide is important for maintaining BMD and fracture protection [101].

There are two other PTH analogs for osteoporosis:

- Full length recombinant PTH 1-84. This injected medication has similar efficacy as teriparatide for osteoporosis [102], but is not widely available or approved for osteoporosis.
- Abaloparatide (recombinant parathyroid hormone-related peptide 1-34) is a newly approved injected medication for severe osteoporosis. Parathyroid hormone-related peptide (PTHrP) shares homology with PTH, but stimulates less bone catabolism and is less potent at increasing serum calcium [103]. Abaloparatide shares 70% homology with human PTHrP but has additional modifications to enhance bone anabolic effect. The ACTIVE trial randomized 2463 postmenopausal women with severe osteoporosis (any age with T score between – 2.5 and – 5.0 plus prior fracture, or age > 65 with prior fracture plus T score between – 2.0 and – 5.0, or age > 65 without fracture plus T score – 3.0 to – 5.0) to abaloparatide 80 mcg, teriparatide 20 mcg, or placebo for 18 months [104•]. There was a significant reduction of new vertebral (RR 0.14, 95% CI, 0.05–0.39) and non-vertebral (RR 0.57, 95% CI, 0.32–1.00) fractures compared with placebo. There was no significant difference in fracture risk compared to teriparatide, but the risk of hypercalcemia was lower (3.4% abaloparatide vs. 6.4% teriparatide). However, more participants in the abaloparatide group (9.9%) discontinued treatment due to adverse events compared with teriparatide (6.8%). This medication is approved in the USA, but it is awaiting regulatory approval in other countries.

Estrogen and SERMs

The Women's Health Initiative trial established estrogen's efficacy in preventing hip and vertebral fractures in postmenopausal women [105]. The trial was terminated early due to an increased risk of coronary artery disease, breast cancer, stroke, and pulmonary embolism in the treatment arm [106]. Therefore, estrogen is not a recommended treatment for osteoporosis. Individuals using hormone replacement therapy for postmenopausal symptoms can benefit from bone protection at the risk of vascular disease and malignancy.

The best studied SERM for osteoporosis is raloxifene, which reduces vertebral fractures but not hip fractures [107]. Bazedoxifene [108] and lasofoxifene [109] also reduce vertebral and non-vertebral fractures, but hip fracture data is not available. This class of medication has the added benefit of reducing breast cancer risk, but they increase rates of venous thromboembolism [110]. In general, other osteoporosis medications should be considered before SERMs. In individuals who wish to concomitantly reduce the risk of breast cancer, SERMs can be considered.

Monitoring and duration of treatment

The American College of Physicians 2017 osteoporosis guidelines recommends 5 years of osteoporosis treatment duration after a first diagnosis. The panel further recommends not performing BMD testing during the initial 5-year period. Both are weak recommendations based on low-quality evidence. The reasons for recommending against monitoring BMD include the (i) absence of RCT evidence showing benefit of monitoring, (ii) observational data showing that a repeat BMD 4 years after diagnosis was not better than baseline BMD in predicting future fractures [111], and (iii) RCT data showing that the incidence of fractures is reduced despite declining BMD in participants [112, 113]. There is debate and uncertainty around this weak recommendation against monitoring BMD. The absence of RCT evidence highlights a need for further studies directly addressing the question. We recommend clinical evaluation and BMD after 1–3 years of therapy to monitor efficacy, adherence, and secondary causes [42]. Those with rapid bone loss or severe osteoporosis may require switching to more potent medications (e.g., from an oral bisphosphonate to denosumab or teriparatide) [42].

The recommendation to limit the initial treatment duration to 5 years is based on studies of bisphosphonates where fracture risk was no different whether the participants received 5 or 10 years of treatment (3 vs. 6 years for zoledronate) [114, 115]. However, individuals at high risk of fractures will benefit from continued therapy [116]. Bisphosphonates remain in the body for long periods even after discontinuation, so this finding is not applicable for other osteoporosis medications.

New therapies

Deeper understanding of osteoporosis pathogenesis enabled the discovery of novel drug targets. One promising target is sclerostin, which is an endogenous protein that inhibits osteoblast-mediated bone formation [117]. Another target is cathepsin K, which is secreted from osteoclasts to dissolve collagen from bone matrix [118]. Odanacatib was a cathepsin K inhibitor in development, but clinical trials were stopped because of increased stroke risk [119].

Romosozumab is a monoclonal antibody directed against sclerostin. Twelve monthly injections of romosozumab followed by 1 year of alendronate was showed to be superior to alendronate alone for 2 years in the ARCH trial (n = 4093) [116]. The risks of vertebral, non-vertebral, and hip fractures were all lower in the romosozumab group. However, there was a higher risk of serious cardiovascular events in the romosozumab group (2.5 vs. 1.9% alendronate), which triggered a deferral of FDA approval for closer examination of the data [120•]. In the larger FRAME trial (n = 7180) comparing 12 months of

romosozumab with placebo, serious cardiovascular events were not different between groups (1.2 vs. 1.1% placebo) [121•]. Bisphosphonates (including alendronate) are hypothesized to be cardioprotective [122], but it is unclear whether this explains the increased risk of romosozumab in the ARCH trial.

Conclusion

As the landscape of osteoporosis continues to change, available evidence will become increasingly complex to interpret. There are numerous effective therapies for fracture prevention, so attention should be shifted to translating evidence into practical knowledge for clinicians. Clinical practice guidelines are essential. Economic evaluations can determine the most cost-effective interventions as health care costs rises with the aging population. Furthermore, fracture prevention at the population level is important, whether through community fall prevention strategies or ways of improving bone health (e.g., smoking cessation and fortified foods).

Compliance with Ethical Standards

Conflict of Interest
Eric Kai-Chung Wong declares that he has no conflict of interest. Alexandra Papaioannou declares that she has no conflict of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance

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