REVIEW

The effects of adjuvant endocrine therapy on bone health in women with breast cancer

Sabashini K Ramchand^{1,2}, Yee-Ming Cheung^{1,2}, Belinda Yeo^{3,4} and Mathis Grossmann^{1,2}

¹Department of Endocrinology, Austin Health, Heidelberg, Victoria, Australia

²Department of Medicine, Austin Health, The University of Melbourne, Heidelberg, Victoria, Australia

³Department of Oncology, Austin Health, Heidelberg, Victoria, Australia

⁴Olivia Newton-John Cancer Research Institute, Heidelberg, Victoria, Australia

Correspondence should be addressed to S K Ramchand: sabashini.ramchand@austin.org.au

Abstract

In women with oestrogen receptor (ER)-positive early breast cancer, oestradiol is important for breast cancer development and progression. Endocrine therapy prevents the deleterious effects of oestradiol in breast tissue by systemically depleting oestradiol concentration (aromatase inhibitors) or preventing its local action in breast tissue (selective oestrogen receptor modulators i.e. tamoxifen), thereby improving oncological outcomes. Use of aromatase inhibitors in postmenopausal women and ovarian function suppression with either tamoxifen or aromatase inhibition in premenopausal women, consequent to systemic oestradiol depletion, exerts detrimental effects on skeletal health. The oestradiol-deficient state causes increased bone remodelling and a negative bone balance. This results in bone loss, microstructural deterioration and bone fragility predisposing to fractures. Similar effects are also seen with tamoxifen in premenopausal women. In contrast, use of tamoxifen in postmenopausal women appears to exert protective effects on bone but studies on fracture risk are inconclusive. The longevity of women with ER-positive breast cancer treated with adjuvant endocrine therapy emphasises the need to mitigate the adverse skeletal effects of these therapies in order to maximise benefit. In general, fractures are associated with increased morbidity, mortality and are a high socioeconomic burden. Whilst the efficacy of antiresorptive therapy in preventing bone mineral density loss in postmenopausal women has been established, further clinical trial evidence is required to provide guidance regarding fracture risk reduction, when to initiate and stop treatment, choice of agent and optimal management of bone health in premenopausal women receiving endocrine therapy. In addition, potential oncological benefits of antiresorptive therapies will also need to be considered.

Key Words

- ▶ bone density
- ▶ breast cancer
- ▶ endocrine therapy
- ▶ fracture
- ▶ oestradiol deprivation

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Introduction

Breast cancer is the most common cancer diagnosed in women worldwide, contributing 25.4% of the total number of new cases diagnosed in 2018 (www.wcrf.org). Due to earlier detection and advances in treatment, the 5-year survival rate in women with early breast cancer is currently greater than 90% ([Early Breast Cancer Trialists'](#)

[Collaborative Group 2015b](#)), emphasising the need to mitigate adverse long-term treatment effects.

Approximately 75% of diagnosed breast tumours express oestrogen receptors (ERs) and are termed ER-positive breast cancers ([Nadji *et al.* 2005](#)). Oestradiol is important for stimulating breast cancer growth and

proliferation and treatment with endocrine therapy, which attempts to prevent proliferative oestradiol signalling in breast cancer cells, is routine care. In addition to its effects on breast cancer cells, oestradiol also plays a vital role in a number of physiological mechanisms including the regulation of bone metabolism (Riggs *et al.* 2002). Adjuvant endocrine therapy significantly reduces the risk of breast cancer recurrence, increasing the likelihood of cure, but due to its systemic effects on oestradiol, it has unintended adverse effects on skeletal health. Concurrent use of gonadotropin-releasing hormone (GnRH) analogues with either tamoxifen or an aromatase inhibitor (AI) in premenopausal women and AIs in postmenopausal women causes accelerated bone loss and increased risk of fracture. Tamoxifen, a selective oestrogen receptor modulator, causes bone loss in premenopausal women but is bone protective in postmenopausal women.

In the general population, fragility fractures adversely affect quality of life, increase morbidity and mortality and are associated with a high socioeconomic burden (Pisani *et al.* 2016). Therefore, minimisation of bone loss and ultimately fracture prevention is a significant survivorship issue that needs to be addressed. This review will discuss the effects of endocrine therapy on skeletal health in women with ER-positive early breast cancer and outline current evidence regarding pharmacotherapy to prevent bone loss and minimise fracture risk in these women. Material discussed is based on peer reviewed publications indexed on the PubMed database, from 1970 to December 2018, using, in various combinations, the search terms 'aromatase inhibitors', 'bisphosphonates', 'bone health', 'denosumab', 'endocrine therapy', 'fracture', 'gonadotropin-releasing hormone', 'osteoporosis', 'selective oestrogen receptor modulators', 'tamoxifen' or 'ovarian function suppression'. Only material relevant to the use of adjuvant endocrine therapy for early breast cancer was included; hence, material pertaining to metastatic breast cancer was excluded. Only full-text articles, published in English, were reviewed.

Biosynthesis of oestrogens and mechanisms of endocrine therapy in early breast cancer

There is accumulating evidence from animal, epidemiological and *in vitro* studies, that endogenous oestrogens play a causal role in the development of breast cancer and its progression (Althuis *et al.* 2004). Endocrine therapy attempts to prevent proliferative oestradiol receptor signalling by either inhibiting binding of oestradiol to its receptor or reducing the concentration of oestradiol.

Biosynthesis of oestrogens

Oestrogens are highly conserved steroid hormones which occur in three main forms: oestrone (E1), 17 β -oestradiol (E2) and oestriol (E3). In premenopausal women, the primary source of oestrogens comes from ovarian production which accounts for >90% of circulating E2, the principal and most potent (biologically active) oestrogen secreted. In postmenopausal women, extra-ovarian production of oestrogens becomes predominant, particularly in stromal adipose tissue (Silva *et al.* 2008), and serum E1 and E2 concentrations fall by approximately 75 and 90% respectively (Albright *et al.* 1941). In postmenopausal women, E1 is the main circulating oestrogen but has weak oestrogenic effects and requires conversion to E2 in order to maximise its effects. E3 is the most prevalent oestrogen in the maternal circulation during pregnancy but exists in extremely low concentrations in the non-pregnant state. A fourth oestrogen, oestetrol (E4), thought to be synthesised exclusively by the foetal liver, is a weak oestrogen with detectable concentrations only during pregnancy. Its biological function is currently unknown.

Ovarian production of oestrogens begins with androgen synthesis in the theca cells and ends with conversion of these androgen substrates to oestrogens by the enzyme aromatase in the granulosa cells. In the theca cells, luteinising hormone (LH) signalling stimulates the expression of steroid-synthesising enzymes that convert cholesterol to the androgens, androstenedione and testosterone (T). In the granulosa cells, follicle-stimulating hormone (FSH) signalling stimulates the expression of aromatase which converts these androgen substrates to oestrogens: androstenedione to E1 and T to E2. Aromatase (CYP19), encoded by the *CYP19A1* gene (Evans *et al.* 1986), is the only known enzyme responsible for the synthesis of oestrogens from androgenic substrates. In healthy humans, aromatase is highly expressed in the placenta and granulosa cells of ovarian follicles but also expressed at lower levels in several other tissues which include the stroma of adipose tissue, muscle, bone, adrenal glands, breast tissue and brain. Other key enzymes involved in the biosynthesis of oestrogens are the 17 β hydroxysteroid dehydrogenases responsible for interconversion of androstenedione and T and of E1 and E2 and steroid sulphatase which catalyses the conversion of oestrone sulphate (inactive form) to E1 (active form) (Fig. 1).

Extra-ovarian synthesis of oestrogens, the predominant source of oestrogens in postmenopausal women, differs from ovarian synthesis in a few distinct ways. First, the majority

on gonadotropin production. This causes activation of the hypothalamic-pituitary-gonadal axis, thereby increasing both ovarian androgen production and aromatase activity which ultimately increases oestradiol concentration (Simpson & Santen 2015). As such, use of AIs in premenopausal women is contraindicated, unless there is concurrent OFS. Tamoxifen, the most commonly used selective oestrogen receptor modulator, acts as an ER antagonist in breast tissue and is effective irrespective of circulating oestradiol concentration. It can therefore be used as monotherapy in both pre- and postmenopausal women (Maximov *et al.* 2013).

Clinical use and oncologic benefits of adjuvant endocrine therapy

The American Society of Clinical Oncology, along with other international societies, recommends the use of endocrine therapy in all women with ER-positive early breast cancer (Burstein *et al.* 2014). There are two important considerations when making adjuvant endocrine therapy decisions: (i) which drug to select at the commencement of endocrine therapy (which is intended for 5-year duration) and (ii) whether to extend endocrine therapy beyond 5 years, and if so, whether to continue the same agent or switch. Extending adjuvant endocrine therapy beyond 5 years is becoming the standard of care for some patients, although identifying those patients with a risk of late relapse remains an area of intense research activity.

Postmenopausal women

In postmenopausal women, AIs are preferred over tamoxifen and are used as monotherapy or sequential therapy after tamoxifen. In a meta-analysis of 9855 women with ER-positive early breast cancer, 10-year breast cancer mortality was lower in women treated with an AI for 5 years compared to women treated with tamoxifen for five years (12.1% vs 14.2%, relative risk (RR) 0.85; 95% CI 0.75–0.96) (Early Breast Cancer Trialists' Collaborative Group 2015b). The difference in mortality benefit between an AI and tamoxifen is modest compared to the larger 9.2% difference in 15-year breast cancer mortality between tamoxifen and placebo (RR 0.70; 95% CI 0.64–0.75) (Early Breast Cancer Trialists' Collaborative Group 2011); hence, tamoxifen is still a reasonable alternative when an AI is contraindicated or not tolerated.

Tamoxifen given for 10 compared to 5 years is preferred due to improved disease-free and overall survival (Davies *et al.* 2013). More recent evidence from multiple randomised controlled trials have addressed the question

of whether extending AI therapy for a further 5 years reduces the risk of recurrence in women who have received AI therapy as part of their initial 5 years of adjuvant treatment. Results from the MA.17R, DATA and NSABP B-42 trials have all demonstrated modest improvements in disease-free survival of 2–4% with no differences in overall survival (Goss *et al.* 2016, Tjan-Heijnen *et al.* 2017, Mamounas *et al.* 2019). Based on subset analyses, women at greater risk of recurrence according to their clinicopathological features derived a larger benefit than women at lower risk. In women who received extended AI therapy, there was an increased risk of AI-induced toxicities which led to decreased compliance (Goss *et al.* 2016). In the MA.17R study, there was almost a doubling in the rate of osteoporosis (11 vs 6%) and a 3.5% absolute increase in fracture rates despite approximately 1 in 2 women receiving treatment with bisphosphonates (Goss *et al.* 2016). These findings are consistent with a recent systematic review of 16,349 women, which demonstrated increased odds of fracture (odds ratio (OR) 1.34; 95% CI 1.16–1.55) with AI treatment beyond 5 years (Goldvaser *et al.* 2018). As such, the use of extended AI therapy is largely considered only in women who have high-risk disease and/or in those with minimal AI-induced toxicity.

Premenopausal women

Until recent years, the standard of care of premenopausal women has been to use upfront tamoxifen and if they remain premenopausal at 5 years, then extending tamoxifen to 10 years is an option as evidence from the aTTom and ATLAS trials (Gray *et al.* 2013, Davies *et al.* 2017). However, in those with high-risk disease, based on a number of clinicopathological characteristics such as younger age, large tumour size and lymph node involvement, recent evidence has demonstrated more favourable oncological outcomes with the use of concurrent OFS with tamoxifen or aromatase inhibition (Burstein *et al.* 2016). Evidence for this approach comes from the combined analysis of two pivotal International Breast Cancer Study Group (IBCSG) initiated phase III randomised controlled trials (RCTs), SOFT and TEXT (Regan *et al.* 2013). In these trials, approximately 6000 premenopausal women were randomised to 5 years of tamoxifen monotherapy or concurrent OFS with either tamoxifen or AI (exemestane) in SOFT and to OFS with either tamoxifen or AI (exemestane) in TEXT (Regan *et al.* 2013).

Results of the 8-year follow-up of these two trials have recently been published (Francis *et al.* 2018). In SOFT, 8-year disease-free survival rates were 78.9% with

tamoxifen alone, 83.2% with OFS+tamoxifen (hazard ratio (HR) 0.76; 95% CI 0.62–0.93 vs tamoxifen alone) and 85.9% with OFS+AI (HR 0.65; 95% CI 0.53–0.81 vs tamoxifen alone) (Francis *et al.* 2018). The rate of overall survival at 8 years was 91.5% with tamoxifen alone, 93.3% with OFS+tamoxifen (HR 0.67; 95% CI 89.4–93.2 vs tamoxifen alone) and 92.1% with OFS+AI (HR 0.85; 95% CI 0.62–1.15 vs tamoxifen alone) (Francis *et al.* 2018). In the combined analysis of SOFT and TEXT, which included all women receiving OFS randomised to either tamoxifen or AI, 8-year disease-free survival rates were 86.8% with OFS+AI compared to 82.8% with OFS+tamoxifen (HR 0.77; 95% CI 0.67–0.90). Despite these improvements in disease-free survival, with OFS+AI compared to OFS+tamoxifen, there is no proven evidence of a survival advantage with the use of OFS+AI compared to OFS+tamoxifen at 8 years; overall survival rates were 93.4 and 93.3% respectively (HR 0.98, 95% CI 0.79–1.22) (Francis *et al.* 2018). Additionally, use of OFS+AI, compared to OFS+tamoxifen, had higher rates of adverse events, including a higher incidence of osteoporosis (14.8 vs 7.2%) (Francis *et al.* 2018). Clinicians will therefore need to consider the benefits versus the toxicities of this more aggressive treatment strategy on an individualised basis.

Oestradiol deficiency and bone loss

Oestradiol is an important regulator of bone metabolism and oestradiol deficiency, such as that produced by menopause, is an important determinant of bone loss, microstructural deterioration and bone fragility (Albright *et al.* 1941, Riggs *et al.* 2002).

Bone modelling and remodelling are the two processes that determine bone's external size, shape and its internal microstructure. Bone modelling is the deposition of bone on a quiescent surface of bone and is responsible for changing the size and shape of bone. Bone remodelling, carried out by teams of cells forming basic multicellular units (BMUs), is responsible for maintaining the material composition of bone (Frost 1964). Osteoclasts of a BMU resorb a volume of bone at a given location and this is followed by a lag or reversal phase and then a phase of bone formation carried out by osteoblasts. Bone formation is characterised by the much slower deposition of osteoid which undergoes rapid primary and then much slower secondary mineralisation to become bone (Boskey 2002, Akkus *et al.* 2003, 2004). The resorptive phase takes ~3 weeks (Eriksen *et al.* 1984b), the reversal

phase ~5 weeks (Eriksen *et al.* 1984b) and the formation phase ~3 months (Tran Van *et al.* 1982, Eriksen *et al.* 1984a) with mineralisation taking months if not years to reach completion (Boskey 2002, Akkus *et al.* 2003, 2004).

To maintain bone mass at the same level, the bone formed in each BMU must replace precisely the amount removed by resorption within that BMU. In states of oestradiol deficiency, bone remodelling becomes unbalanced and rapid. There is a net decrease in the amount of bone deposited by each BMU and an increase in the rate of bone remodelling, i.e., greater numbers of BMUs, each deposit less bone than they remove producing a net bone loss and microstructural deterioration (Lips *et al.* 1978, Vedi *et al.* 1983–1984, Eriksen 1986). The molecular and cellular mechanisms by which the skeletal effects of oestradiol deficiency are mediated are complex and incompletely understood. These mechanisms are reviewed in Almeida *et al.* (2017) and Khosla & Monroe (2018).

Unbalanced and rapid remodelling causes bone loss and structural deterioration of both trabecular and cortical bone. Increased resorption depth upon trabeculae cause them to perforate and become disconnected (Hernandez *et al.* 2006). Resorption of cortical bone initiated at points upon the surfaces of Haversian canals causes them to enlarge, coalesce and fragment the cortex. The microstructural deterioration of the reduced bone volume compromise bone strength out of proportion to the bone loss producing it and increase the risk of fragility fractures (Schaffler & Burr 1988, Hernandez *et al.* 2006) (Fig. 2).

Endocrine therapy and bone health

Endocrine therapy, apart from tamoxifen in postmenopausal women, causes relatively rapid decreases in circulating oestradiol concentrations or competitively inhibits oestradiol action in bone, adversely affecting bone health in the majority of women with early breast cancer.

Selective oestrogen receptor modulators

In contrast to its action as a pure ER antagonist in breast tissue, SERMs, most commonly tamoxifen, act as partial ER agonists in bone and their actions depend on menopausal status as tamoxifen is less potent than native oestradiol (Maximov *et al.* 2013).

In postmenopausal women where endogenous oestradiol concentrations are low, tamoxifen acts as a

Figure 2

Effect of oestradiol deficiency on bone structure. Representative cross-sectional high-resolution peripheral quantitative computed tomography images of the distal radius in an age-matched healthy premenopausal woman (control – left panel) and a premenopausal woman with ER-positive early breast cancer treated with concurrent ovarian function suppression and aromatase inhibition (case–right panel). Panel A: Loss of trabecular number and increased trabecular separation in the case compared to the control. Panel B: Increased bone resorption at the cortico-medullary interface resulting in thinning and fragmentation of the cortex.

partial agonist in bone, preventing bone loss and reducing fracture risk. In a small study of 140 postmenopausal women, tamoxifen modestly increased annual lumbar spine bone mineral density (BMD) by 0.6% compared to a 1.0% decrease in the placebo group (Love *et al.* 1992). In the National Surgical Adjuvant Breast and Bowel Project P-1 Study, 13,388 women deemed high risk of developing breast cancer were randomised to 5 years of tamoxifen 20mg daily or placebo (Fisher *et al.* 2005). After a 7-year follow-up period, women treated with tamoxifen for 5 years had a 32% reduction in osteoporotic fractures compared to placebo (RR 0.68; 95% CI 0.51–0.92) (Fisher *et al.* 2005). This is in contrast to findings of a recent meta-analysis that reported similar fracture risk in women with breast cancer treated and not treated with tamoxifen (pooled risk ratio 0.95; 95% CI 0.84–1.07) (Tseng *et al.* 2018).

In premenopausal women in whom circulating oestradiol concentrations are high, tamoxifen acts as a partial antagonist in bone, competing with oestradiol for the ER-binding sites and causes bone loss (Powles *et al.* 1996). In a 3-year placebo-controlled prospective study, the average annual loss in lumbar spine BMD in premenopausal women treated with tamoxifen was 1.4% compared to a 0.2% gain with placebo. However, when combined with the GnRH analogue goserelin, which significantly reduces circulating oestradiol concentration by >90%, tamoxifen appeared to mitigate the bone loss associated with goserelin induced OFS (Sverrisdottir *et al.* 2004). In a 2-year RCT of 89 women, total body BMD

decreased by 5.0% with goserelin monotherapy compared to 1.4% with combined goserelin and tamoxifen (Sverrisdottir *et al.* 2004).

Aromatase inhibitors

Postmenopausal women treated with AIs, compared to age-matched women, have increased bone remodelling, accelerated bone loss and increased fracture rates. Although preclinical studies have suggested a bone sparing effect of exemestane, due to its androgenic structure, compared to letrozole (Goss *et al.* 2004), the few clinical studies that have compared the effects of different AIs on bone, have not revealed any significant differences amongst them (Goss *et al.* 2014, Smith *et al.* 2017).

In a systematic review based meta-analysis of 30,023 postmenopausal women from seven RCTs, there was a 47% increased fracture risk in women treated with AIs compared to tamoxifen (OR 1.47; 95% CI 1.34–1.61) (Amir *et al.* 2011). Fracture incidence was 7.5% and 5.2% in the AI and tamoxifen group respectively, with a number needed to harm of 46 (Amir *et al.* 2011). However, the absence of studies that investigated the effect of these endocrine therapies on fracture risk as an adjudicated primary endpoint, the lack of placebo control groups, and the potential beneficial effects of tamoxifen on bone in postmenopausal women make interpretation problematic. Indeed, in a dedicated fracture endpoint trial in 3420 postmenopausal women, approximately 1 in 10 women had an incident clinical fracture within three years of

AI treatment (Gnant *et al.* 2015), comparable to fracture rates reported in untreated women 5–10 years older with established osteoporosis (Lyles *et al.* 2007, Cummings *et al.* 2009). The much higher fracture incidence in this study compared to reports from the majority of primary AI efficacy trials is consistent with under-reporting of fracture outcomes in these oncology endpoint trials. A systematic review based meta-analysis combining RCTs and cohort studies, estimated a 17% (95% CI 1.07–1.28) increase in fracture risk in women treated with AIs compared to untreated women (Tseng *et al.* 2018). In another recent meta-analysis that compared treatment toxicities in 16,349 postmenopausal women who either received extended AI therapy after an initial five years of AI or placebo/no treatment after an initial five years of AI (Goldvaser *et al.* 2018), extended AI treatment was associated with increased odds of clinical fractures (OR 1.34; 95% CI 1.16–1.55) (Goldvaser *et al.* 2018).

In premenopausal women, as discussed earlier, AIs cannot be used without concurrent OFS. Combined use of OFS and AI in premenopausal women results in a profound reduction in oestradiol concentration and produces the largest magnitude of bone loss in women receiving endocrine therapy. In general, although direct comparisons cannot be made across studies, relative rates of bone loss, as measured by dual-energy x-ray absorptiometry (DXA), are highest in premenopausal women with the greatest degree of oestradiol suppression. Rates of annual BMD loss at the lumbar spine have been reported to be 5.6% with OFS+tamoxifen (Gnant *et al.* 2008), 8.2% with GnRH monotherapy (Fogelman *et al.* 2003), and 9.3% with OFS+AI (Gnant *et al.* 2008). In the SOFT and TEXT trials, use of OFS+AI was associated with a two-fold increase in the prevalence of osteoporosis compared to OFS+tamoxifen (13.2 vs 6.4% at 68 months) (Pagani *et al.* 2014). In a small cross-sectional study of premenopausal women (mean age 43 years) with early breast cancer treated with OFS+AI for a median duration of 17 months (range 6–120), cortical and trabecular volumetric BMD, assessed by high-resolution peripheral quantitative computed tomography (HR-pQCT), was markedly reduced compared to healthy age-matched controls and similar to women 20 years older who were at least 10 years post natural menopause (Ramchand *et al.* 2017).

A small number of clinical trials have reported increases in BMD in premenopausal women who resume menstrual function after cessation of OFS+AI (Gnant *et al.* 2008) and in postmenopausal women after cessation of AI (Geisler *et al.* 2006). Use of bone densitometry obscures the differing behaviour of bone matrix volume

and matrix mineralisation and may produce misleading information. It is not known if the increase in BMD, observed after cessation of aromatase inhibition, is due to an increase in bone matrix volume or an increase in matrix mineralisation of the existing volume. It is more likely that cessation of aromatase inhibition reduces the bone remodelling rate, allowing for increased mineralisation of the less frequently remodelled matrix volume as opposed to an accrual of matrix volume (Seeman 2010). The effects on bone strength and fracture risk are also not known but will differ depending on the underlying process causing the increase in BMD.

Management of bone health in women receiving endocrine therapy

Several guidelines and position statements regarding the assessment and management of bone health in women with ER-positive early breast cancer treated with endocrine therapy have been developed by international societies (Gralow *et al.* 2013, Paterson & Shea-Budgell 2013, Coleman *et al.* 2014, Juozaityte *et al.* 2014, Singapore Cancer Network Breast Cancer 2015, Hadji *et al.* 2016, 2017, Tremollieres *et al.* 2017, Grossmann *et al.* 2018).

Evaluation and monitoring

All women commencing AIs and premenopausal women commencing tamoxifen should have a baseline evaluation of their fracture risk. This should include a detailed history, physical examination, laboratory evaluation and BMD assessment by DXA, to screen for risk factors for fracture. Standard risk factors for osteoporosis include advancing age, prevalent fragility fractures, parental history of hip fracture, low body mass index, tobacco smoking, excessive alcohol consumption, chronic glucocorticoid use and inflammatory joint conditions such as rheumatoid arthritis. Assessment for morphometric vertebral fractures by thoraco-lumbar x-ray may be considered in postmenopausal women and premenopausal women with low BMD (T or Z score <−1.5) (Bouvard *et al.* 2012, Pedersini *et al.* 2017). Use of conventional fracture risk assessment tools such as FRAX and the GARVAN Fracture Risk Calculator may underestimate fracture risk as they do not account for AI therapy or chemotherapy. These tools are also not validated for use in women less than 40 years of age.

There is no high level evidence to guide the optimal approach to monitor women receiving endocrine therapy.

Assessment of BMD in untreated women should be performed at baseline and may be considered 12 months after starting endocrine therapy with subsequent scans determined on an individualised basis, depending on the presence of clinical risk factors for osteoporosis and baseline BMD values (Grossmann *et al.* 2018). For women treated with antiresorptive therapy, BMD should be assessed at baseline and every two years or less frequently. If there are major changes to clinical status, treatment or significant declines in BMD (annual BMD loss $\geq 5\%$ and/or $\geq 0.05 \text{ g/cm}^2$), women should be re-evaluated and in those women with a decline in BMD, additional assessment regarding treatment adherence, drug absorption and causes of secondary osteoporosis should be undertaken.

Treatment

All women should be advised to adopt lifestyle changes that promote skeletal and overall health. Extrapolating from evidence outside of the breast cancer population given the paucity of evidence specific to women with breast cancer, weight bearing exercise, which includes impact and resistance training, adequate daily calcium intake preferably through dietary sources, vitamin D sufficiency and smoking cessation are routinely recommended.

Similar to recommendations for the general female population, antiresorptive therapy should be commenced in all women with pre-existing fragility fractures and in women 70 years and older who have evidence of osteoporosis on BMD (defined as a T-score < -2.5 S.D.). Outside of these criteria, the optimal threshold at which to commence bone-modifying therapy is unclear. Most guidelines, largely based on expert opinion, would recommend commencing antiresorptive therapy in postmenopausal women with T-scores (or Z-scores if 50 years or younger) less than -2.0 at any site, if annual BMD loss is $\geq 5\%$ and/or $\geq 0.05 \text{ g/cm}^2$, considering baseline BMD and other risk factors for fracture, or in those with increased absolute fracture risk based on the presence of other clinical risk factors other than BMD. In premenopausal women, there is very limited evidence to guide accurate assessment of fracture risk or long-term effects of antiresorptive therapy on skeletal health. The potential for future maternity also needs to be taken into account if antiresorptive therapy is being considered.

Antiresorptive therapy

Postmenopausal women The Food and Drug Administration (FDA) approved antiresorptive therapies

for postmenopausal osteoporosis also have proven efficacy in slowing or preventing AI-induced bone loss in postmenopausal women, based largely on BMD studies (see Grossmann *et al.* 2018 for summary). Of these therapies, zoledronic acid is the best studied. There is limited data on the anti-fracture efficacy of antiresorptive therapies with most bisphosphonate trials underpowered to assess fracture prevention and only one trial examining the effect of denosumab, a RANK-ligand inhibitor, on fracture outcomes (Gnant *et al.* 2015). In this study, denosumab 60mg given 6 monthly, halved the clinical fracture risk at 36 months (estimated fracture rates in the denosumab group 9.6 vs 5.0% in the placebo group) (Gnant *et al.* 2015). The predominant sites of fracture were the forearm and hands (2.6 vs 1.5% in the placebo and denosumab groups respectively) followed by the vertebrae (1.5 vs 1.0% in the placebo and denosumab groups) (Gnant *et al.* 2015). Benefits in fracture risk reduction with denosumab appeared similar irrespective of baseline BMD values although the study may have been underpowered for this analysis (Gnant *et al.* 2015) (Table 1).

Four independent trials (ZO-FAST, Bundred *et al.* 2008; Z-FAST, Brufsky *et al.* 2007; E-ZO-FAST, Llombart *et al.* 2012; NCCTG-NO3CC, Hines *et al.* 2009) evaluated the effects of giving zoledronic acid 4mg 6-monthly at the start of AI therapy or delaying treatment. These studies all demonstrated beneficial effects on BMD with upfront compared to delayed therapy. In the largest study, ZO-FAST, approximately 1000 postmenopausal women were randomised to receive zoledronic acid 4mg 6-monthly when they started AI therapy or treatment was delayed until the women either had a fragility fracture or on study T-score < -2.0 SD (Bundred *et al.* 2008). At 12 months, lumbar spine BMD, the primary endpoint of the study, increased by 2.1% in the women who received immediate treatment compared to a 3.5% decrease in those who received delayed treatment. At 5-year follow-up of the study, there were persistent beneficial effects on BMD in women who received immediate zoledronic acid compared to those who received delayed treatment (lumbar spine BMD increased by 4.3% in the immediate group and decreased by 5.4% in the delayed group, $P < 0.0001$) (Coleman *et al.* 2013). Three-year fracture incidence was similar between the two groups (26 (5.0%) in the immediate group and 32 (6.0%) in the delayed group, $P = 0.502$) (Eidtmann *et al.* 2010). However, this study was not designed to assess fracture outcomes as a primary endpoint and may be underpowered to detect any differences in fracture incidence between the two groups. There were three confirmed and two possible

Table 1 Antiresorptive agents used to treat bone loss in postmenopausal women with ER-positive early breast cancer treated with aromatase inhibitors.

Agent	Dose and frequency	Route	Prevents/reduces BMD loss	Proven anti-fracture efficacy	Proven oncological benefit
Alendronate	70 mg, QW	PO	Yes	No	No
Clodronate	1600 mg, QD	PO	Yes	No	Yes
Ibandronate	150 mg, Q4W	PO	Yes	No	No
Risedronate	35 mg, QW	PO	Yes	No	No
Zoledronic Acid	4 mg, Q6M	IV	Yes*	No	Yes
Denosumab	60 mg, Q6M	SC	Yes	Yes	No

Data are based on evidence from randomised controlled trials and meta-analyses. All data are specific to postmenopausal women treated with aromatase inhibitors unless otherwise specified.

*Zoledronic acid 4 mg Q6M prevents BMD loss in both postmenopausal women treated with aromatase inhibitors and premenopausal women treated with concurrent OFS + AI.

BMD, bone mineral density; IV, intravenous; PO, per oral; SC, subcutaneous.

cases (insufficient data) of osteonecrosis of the jaw (ONJ) in women receiving zoledronic acid (Coleman *et al.* 2013).

Premenopausal women In premenopausal women, there are very few studies evaluating the efficacy of antiresorptive therapy in preventing endocrine therapy induced bone loss and no studies assessing fracture outcomes. In the largest RCT of 404 women, the efficacy of zoledronic acid in preventing BMD loss at 36 months was assessed (Gnant *et al.* 2008). In this study, women were treated with OFS and either tamoxifen or AI. In each of the OFS+tamoxifen and OFS+AI groups, women were randomised to receive either zoledronic acid 4 mg 6-monthly or placebo. At 36 months, lumbar spine BMD decreased in women receiving placebo by 9.0% (mean difference -0.095 g/cm^2 (-0.134 to -0.057), $P < 0.0001$) and 13.6% (mean difference -0.067 g/cm^2 (-0.179 to -0.102), $P < 0.0001$) in the OFS+tamoxifen and OFS+AI groups respectively, whilst women treated with zoledronic acid had stable BMD at 36 months (Gnant *et al.* 2008). There were no adjudicated cases of ONJ in this premenopausal cohort of women treated with zoledronic acid 4 mg every 6 months for a duration of 3 years (Gnant *et al.* 2008).

Duration of therapy

Evidence regarding the optimal duration of antiresorptive therapy specific to women with early breast cancer receiving endocrine therapy is lacking. Most guidelines suggest treatment cessation at the completion of endocrine therapy unless high fracture risk persists. Given that in contrast to bisphosphonates, denosumab is not retained in bone, soon after cessation of treatment, there is a rapid rise in bone remodelling, a decline in BMD and, although the absolute risk is low, an increased risk of multiple vertebral fractures (Bone *et al.* 2011, Miller *et al.* 2011). *Post hoc* analysis of the large denosumab trials, FREEDOM

and FREEDOM Extension, showed that women at the greatest risk of developing multiple vertebral fractures were those who had a prior vertebral, either before or during treatment (Cummings *et al.* 2018). Additionally, preclinical data have demonstrated the importance of the bone microenvironment in cancer progression and increased bone remodelling has been shown to release factors that stimulate tumour growth (Croucher *et al.* 2016). Therefore, current expert opinion recommends that delays in subsequent dosing of denosumab should be avoided and that cessation of denosumab is consolidated with a bisphosphonate (Tsourdi *et al.* 2017, Chukir *et al.* 2018). Data regarding optimal route, duration and timing of bisphosphonate therapy after cessation of denosumab is currently under investigation.

Anti-cancer role of antiresorptive drugs

The importance of the bone microenvironment in cancer development and progression is now widely recognised. Through a number of complex mechanisms, which remain incompletely understood, tumour cells lie dormant in bone and in some cases reactivate to produce metastasis (Croucher *et al.* 2016). Remodelling of the endosteal bone surface is thought to be one mechanism by which dormant tumour cells are reactivated (Croucher *et al.* 2016). The efficacy of adjuvant zoledronic acid and oral bisphosphonates, which slow bone remodelling, in preventing disease recurrence has been evaluated in a number of small breast cancer clinical trials. With the exception of a few studies, these trials were predominantly negative for this outcome. However, the patient-level meta-analysis conducted by the Early Breast Cancer Trialists Collaborative Group (EBCTG), which predominantly included studies that evaluated clodronate or zoledronic acid with very limited data for other bisphosphonates, demonstrated that in the sub-group

of women who were postmenopausal (either natural or iatrogenic), both zoledronic acid (4 mg 6-monthly) and clodronate reduced breast cancer mortality (RR 0.82; 95% CI 0.73–0.93) and bone recurrence (RR 0.72; 95% CI 0.60–0.86) (Early Breast Cancer Trialists' Collaborative Group 2015a). No beneficial effects on mortality or breast cancer recurrence were noted in the premenopausal subgroup (Early Breast Cancer Trialists' Collaborative Group 2015a). The difficulty with extrapolating the results of this meta-analysis to clinical care was the observation that all postmenopausal women, irrespective of their ER or lymph node status, appeared to benefit from adjuvant zoledronic acid or clodronate, making it difficult to select women for whom this treatment would be most beneficial.

Although there was a signal of improved disease-free survival in the intention to treat analysis of the ABCSG-18 trial (Gnant *et al.* 2015), a fracture outcome trial where postmenopausal women were randomised to denosumab 60 mg 6-monthly or placebo for a 3-year period, results of the recently completed but not yet peer-reviewed phase III D-CARE trial (Coleman *et al.* 2018) were in contradiction to these findings. In the D-CARE trial, the dosing regimen of denosumab differed significantly from the ABCSG-18 trial. In D-CARE, postmenopausal women with ER-positive early breast cancer received 120 mg of denosumab or matching placebo every month for 6 months and then every 3 months for up to 5 years (Coleman *et al.* 2018). After median follow-up of 67 months, there were no reductions in bone metastasis-free survival (BMFS), breast cancer recurrence, or mortality in postmenopausal women treated with denosumab compared to placebo (Coleman *et al.* 2018). Whilst this was a negative study for its primary outcome (BMFS), exploratory analysis suggested benefit with denosumab for time to bone metastasis as first recurrence (HR 0.76; 95% CI 0.59–0.97) (Coleman *et al.* 2018). These findings were unexpected as denosumab is thought to be a more potent inhibitor of bone remodelling compared to zoledronic acid or clodronate. As anticipated, given the higher cumulative doses of denosumab in the D-CARE trial, incidence rates of ONJ and atypical femoral fractures (AFF) were higher in D-CARE compared to ABCSG-18. In D-CARE, ONJ occurred in 122 (5.4%) women treated with denosumab compared to 4 (0.2%) women receiving placebo and AFF only occurred in women receiving denosumab, $n=9$ (0.4%) (Coleman *et al.* 2018). There were no independently adjudicated cases of ONJ and/or confirmed AFF in ABCSG-18 (Gnant *et al.* 2015).

Expert societies, including the American Society of Clinical Oncology, currently recommend the use of

zoledronic acid 4 mg 6-monthly or clodronate as adjuvant treatment in postmenopausal women with early breast cancer, outside of their role in maintaining bone health and preventing fractures (Dhesy-Thind *et al.* 2017). The absolute oncological benefits appear to be greater in women who are at higher risk of breast cancer recurrence and almost all women included in the trial data supporting this recommendation had received systemic therapy (Dhesy-Thind *et al.* 2017).

Anabolic therapy

Currently available anabolic agents, teriparatide and abaloparatide, are not approved for use in women with breast cancer due to theoretical concerns of stimulating cancer cell progression. Additionally, in women who are treated with radiotherapy where the field of radiation includes the ribs, teriparatide cannot be used as the risk of osteosarcoma is increased in these women. Novel anabolic agents, such as dickkopf-1 and sclerostin inhibitors, have predominantly been studied in multiple myeloma and cancer metastasis (Lovato & Lewiecki 2017). Their utility and safety in women treated with endocrine therapy has not been evaluated.

Conclusion

The longevity of women with ER early positive breast cancer emphasises the importance of mitigating long-term adverse treatment effects on skeletal health. The majority of studies that have evaluated the effects of endocrine therapy on bone health in women with early breast cancer are short-term, most 3 years or less, and based largely on BMD data. Consequently, for premenopausal women in particular, long-term treatment effects on bone quality and fracture risk remain unknown. The effect of treatment cessation on skeletal health is another area that warrants further study. BMD assessment by DXA also has limitations. BMD changes cannot capture the changes in microstructure that occur with endocrine therapy or identify changes in bone volume and matrix mineralisation as two separate entities. Accurate evaluation of these properties is important because they have different effects on bone quality and fracture risk.

There is also a paucity of data to make firm recommendations regarding appropriate fracture risk assessment and ongoing surveillance of bone health in women receiving endocrine therapy. It is increasingly accepted that standard fracture risk assessment tools underestimate fracture risk in women receiving

endocrine therapy. Moreover, the clinical utility of bone remodelling markers or alternative imaging techniques such as HR-pQCT, in fracture risk assessment and in monitoring treatment response requires further study.

The threshold at which to start bone modifying therapy is also unclear. Whilst most expert societies have suggested a lower treatment threshold in women treated with endocrine therapy (BMD T-score <-2.0 , fragility fracture or the presence of multiple clinical risk factors for secondary osteoporosis) compared to conventional osteoporosis treatment thresholds (BMD T-score <-2.5 or fragility fracture), recent evidence, albeit from a single RCT (Gnant *et al.* 2015) has suggested anti-fracture benefit with antiresorptive therapy in postmenopausal women with a normal BMD T-score (>-1.0). The effect of applying these same thresholds to premenopausal women has not been studied. Finally, the optimal choice of antiresorptive agent, dosing schedule and treatment duration also remain unanswered questions that warrant further study.

Overall, the effect of severe oestradiol depletion on the skeleton is an important clinical consideration that is best managed with a multidisciplinary model of care. Further research in this area should provide information necessary to formulate evidence-based treatment approaches that improve health outcomes in breast cancer survivors.

Declaration of interest

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