

REVIEW

Maintaining bone health by estrogen therapy in patients with advanced prostate cancer: a narrative review

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Abstract

The purpose of androgen deprivation therapy (ADT) in prostate cancer (PCa), using luteinizing hormone-releasing hormone agonists (LHRHa) or gonadotrophin-releasing hormone antagonists, is to suppress the levels of testosterone. Since testosterone is the precursor of estradiol (E2), one of the major undesired effects of ADT is the concomitant loss of E2, causing among others an increased bone turnover and bone loss and an increased risk of osteoporosis and fractures. Therefore, the guidelines for ADT indicate to combine ADT routinely with bone-sparing agents such as bisphosphonates, denosumab or selective estrogen receptor modulators. However, these compounds may have side effects and some require inconvenient parenteral administration. Co-treatment with estrogens is an alternative approach to prevent bone loss and at the same time, to avoid other side effects caused by the loss of estrogens, which is the topic explored in the present narrative review. Estrogens investigated in PCa patients include parenteral or transdermal E2, diethylstilbestrol (DES), and ethinylestradiol (EE) as monotherapy, or high-dose estetrol (HDE4) combined with ADT. Cardiovascular adverse events have been reported with parenteral E2, DES and EE. Encouraging effects on bone parameters have been obtained with transdermal E2 (tE2) and HDE4, in the tE2 development program (PATCH study), and in the LHRHa/HDE4 co-treatment study (PCombi), respectively. Confirmation of the beneficial effects of estrogen therapy with tE2 or HDE4 on bone health in patients with advanced PCa is needed, with special emphasis on bone mass and fracture rate.

Key Words

- ▶ androgen deprivation therapy (ADT)
- ▶ bone health
- ▶ estrogen therapy (ET)
- ▶ transdermal estradiol (tE2)
- ▶ estetrol (E4)

Endocrine Connections
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Introduction

Prostate cancer (PCa) is the second most frequently diagnosed cancer in men worldwide. For decades, androgen deprivation therapy (ADT) has been the cornerstone of treatment for various stages of locally

advanced or metastatic PCa (1, 2). Nearly half of men diagnosed with PCa will undergo ADT at some time after diagnosis and remain on it often for many years or even lifelong (3). Currently, mainly injectable luteinizing

hormone-releasing hormone (LHRH) agonists such as triptorelin, leuprolide and goserelin are used as ADT (4). More recently, gonadotrophin-releasing hormone (GnRH) antagonists such as degarelix and relugolix have been developed (1, 5). At present, ‘Standard of Care’ for advanced or metastatic PCa is ADT in combination with androgen receptor signaling inhibitors, radiotherapy and/or chemotherapy (6).

The purpose of ADT is to suppress the major driver of PCa tumor growth testosterone as much as possible (7). The suppression of testosterone causes loss of libido and sexual function as major side effects. However, no testosterone also means no estradiol (E2), since all E2 in the human body is synthesized by aromatization of its precursor testosterone. Since E2 is by far the most potent and important estrogen in men, ADT causes serious estrogen deficiency, which is heavily underestimated and results in subjective symptoms such as hot flushes and sweats, arthralgia, fatigue, mood changes and depression, sleep disturbances, cognition problems and memory loss (8). Reducing those estrogen deficiency-related symptoms has the potential to make ADT more tolerable and can therefore increase treatment adherence. Furthermore, objective signs of estrogen deficiency occur, such as bone loss, an increased risk of cardiovascular events, sarcopenia, weight gain and metabolic syndrome. Altogether, the side effects of ADT other than those affecting sexuality are more related to the loss of E2 than to the loss of testosterone (Table 1).

With improving survival rates of patients with advanced PCa, one of the major and serious consequences of ADT and the concomitant loss of E2 is increased bone turnover, causing bone loss, osteoporosis and fractures (9, 10, 11). Hip fractures are associated with higher all-cause mortality during and following ADT (12). Therefore, the European guidelines advice to offer long-term ADT users

assessment and follow-up of bone mineral density (BMD) or anti-resorptive therapy with bone-sparing agents (BSAs), especially to those with increased risk factors (low BMD, increased bone loss during ADT). BSAs used for this purpose are bisphosphonates, denosumab or selective estrogen receptor modulators (SERMs) (13). However, these compounds may have side effects. Both short-term (e.g. hypocalcemia or ocular inflammation) and long-term (e.g. osteonecrosis or atrial fibrillation) adverse events (AEs) have been reported for bisphosphonates (14). Apart from its inconvenient parenteral administration, denosumab is considered relatively safe (15). In PCa patients, gastrointestinal and cardiovascular AEs have been reported for SERMs (16).

Estrogen monotherapy or co-treatment of ADT may serve as an alternative approach (17, 18, 19), while beneficial effects on bone are known for (transdermal) E2 (20, 21), diethylstilbestrol (DES) (22), ethinylestradiol (EE) (23) and the natural fetal estrogen estetrol (E4) (24, 25).

In the present narrative review, we limited ourselves to report the observed effects of estrogens on bone health in patients with advanced PCa, taking potential estrogen side effects into consideration.

Search strategy and selection criteria

Extensive literature searches in PubMed were performed by using the combinations of the terms ‘androgen deprivation therapy’ AND bone AND ‘prostate cancer’ with ‘estrogen’, ‘estradiol’ or ‘estetrol’. In addition, searches were performed for the combinations ‘testosterone’, ‘estrogen’, ‘bone’ AND ‘prostate cancer’. Relevant search results were also checked for additional references, but we limited ourselves to publications in English. Publications referring to calcium and vitamin D supplementation were not included. The references identified for the present study cover a period up to March 2022.

Table 1 Side effects of androgen deprivation therapy with, in parentheses, whether it is due to the loss of testosterone (T) or estrogens (E).

‘Big four’	What you see	What is not visible	What the patient feels
Libido loss (T)	Weight gain (E)	Loss of bone, decreased bone mineral density and increased fracture risk (E)	Fatigue (T and E)
Erection problems (T)	Gynecomastia (T and E)	Metabolic syndrome (E)	Sleeping problems (T and E)
Hot flushes and sweating (E)	Muscle atrophy (sarcopenia) (T and E)	Anemia (E)	Loss of energy (T and E)
Arthralgia (joint pain); a frequent and neglected symptom (E)	Decreased size penis and testicles (T)	Increased cardiovascular risk (loss of E)	Apathy (T and E)
	Change in hair pattern (T)		Mood changes and depression (E) Cognition and memory problems (E)

General remarks on bone health in prostate cancer patients

Bone health in PCa patients is influenced by a number of risk factors. Usually, patients with metastasized or infiltrating PCa are at advanced age and may suffer from age-related hypogonadism. Other risk factors include reduced body weight, alcohol intake and vitamin D deficiency. All of this may result in reduced bone density (osteopenia) and if severe enough, in osteoporosis, leading to an increased risk of fracture (26).

The use of ADT will result in (further) loss of bone mineral density (BMD), while treatment with an androgen receptor inhibitor such as abiraterone will require combined treatment with glucocorticoids, putting bone health even more at risk (27). Consequently, the prevalence of osteoporosis in patients with nonmetastatic castration-resistant PCa (CRPCa) is as high as 53% (26).

The awareness of bone health in PCa is increasing, and guidelines and standards for the assessment and treatment of bone loss have recently been created (28, 29). It is advised that a baseline assessment should be made for each patient starting ADT by using a fracture risk assessment tool (FRAX) scoring and bone densitometry. High doses of bisphosphonates, denosumab and SERMs are used in metastatic PCa for the prevention of pathological fractures, radiation of bone metastases, compression of the spinal cord and surgery of bone complications. Lower doses of these BSAs are used for the protection of bone loss and the prevention of osteoporotic fractures during ADT, as summarized by Joseph *et al* (13). The interest in using estrogens as BSA is increased due to their multiple additional benefits such as vasomotor stability (21).

Role of sex hormones in male bone remodeling and ADT-induced bone loss

Bone formation and resorption (bone remodeling) is a complex process regulated by systemic hormones and local regulators produced within the bone (30). Estrogens and androgens are critical for skeletal development and maintenance and play important roles in males and females during the pubertal growth spurt and in reaching peak BMD. Many studies have shown that estrogens are key regulators of bone metabolism not only in women but also in men (21, 30, 31).

In males, both testicular Leydig and Sertoli cells synthesize estrogens with local effects, whereas most estrogens in the blood come from aromatization of testosterone in peripheral organs, particularly in adipose

tissue, muscle, bone and brain. In both males and females, estrogens act upon binding either to two estrogen receptor isoforms (ERs), ER α and ER β ; the complexes then modulate nuclear transcriptional responses as well as extranuclear kinase and G-protein signaling (32). In males, androgen receptors and ERs are expressed not only in bone but also in the reproductive tract, the cardiovascular system, brain, liver, adipose tissue, pancreatic islets and skeletal muscle (33). The discovery that genetic mutations leading to ER and aromatase deficiency cause severe osteoporosis provided essential information about the importance of estrogens for bone metabolism in men. Men with ER mutations or without ER α have a very low BMD in the presence of high levels of circulating estrogens and normal testosterone (34). Case reports of three men with aromatase deficiency showed that they were estrogen-deficient and had a very low BMD (35). When these men received estrogen replacement therapy, it resulted in a marked increase in BMD.

The relative contributions of testosterone and estrogen in regulating bone resorption and formation have been studied in 59 healthy elderly men with a mean age of 68 years (36). In this study, bone metabolism was investigated first under the conditions of physiological testosterone and estrogen replacement and then by assessing the impact on bone turnover of withdrawing both testosterone and estrogen, withdrawing only testosterone, or only estrogen, or continuing both. Bone resorption markers increased significantly in the absence of both hormones, while these were unchanged in men receiving both hormones. By a two-factor ANOVA model, it was shown that estrogen played a major role in preventing the increase in the bone resorption markers, whereas testosterone had no significant effect. By contrast, the bone formation marker serum osteocalcin decreased in the absence of both hormones, and both testosterone and estrogen maintained osteocalcin levels. The authors suggested that in aging men, estrogen is the dominant sex steroid in regulating bone resorption, whereas both testosterone and estrogen are important in maintaining bone formation. More evidence for the important role of estrogens in bone health of older men comes from several large studies showing that low levels of E2 and high levels of sex hormone-binding globulin (SHBG) are associated with reduced BMD, the occurrence of osteoporosis and an increased risk of fractures (31, 37, 38).

In PCa patients, the hypoestrogenic state induced by ADT leads to an increase in bone turnover and a five- to ten-fold increase in the rate of areal BMD loss (9, 10, 39). As alternative to existing BSAs (13), bone health can

be preserved and/or restored by the concomitant use of estrogens (21, 25) or by estrogen monotherapy reaching castration levels of testosterone (20).

Estrogens as bone-sparing agents in patients with advanced prostate cancer

Estradiol

According to Russell *et al.*, there is renewed interest in revisiting E2 as treatment for advanced PCa, especially in view of its additional beneficial role in vasomotor stability and in skeletal maturation and maintenance (21). However, so far, there are only few studies in PCa patients treated with ADT, reporting specifically the efficacy of estrogens in preventing bone loss. The effect of the parenteral estrogen polyestradiol phosphate (PEP) as ADT has been compared with combined androgen deprivation (CAD) with oral flutamide and either triptorelin or bilateral orchidectomy on an optional basis. At the final evaluation of the trial, 855 of the 910 patients died. There was no difference between the treatment groups in terms of biochemical or clinical progression-free survival or in overall or disease-specific survival. Also, there was no difference in cardiovascular (CV) mortality but a significant increase in non-fatal CV events in the PEP arm ($P < 0.05$), predominantly caused by an increase in ischemic heart disease and heart decompensation events. There were 18 severe skeletal events in the CAD group and none in the PEP group ($P = 0.001$) (40).

The CV safety and efficacy of transdermal E2 (tE2) at doses up to 100 μg E2 per day have been established in postmenopausal women (41). The impact of tE2 on BMD was investigated by Ockrim *et al.* in 20 PCa patients (42). Patches were applied to reach E2 levels > 1 nmol/L. After a median follow-up of 15 months (range, 12–20), significant improvements were observed for BMD of the lumbar spine (LS) and hip ($P = 0.05$ and $P = 0.031$, respectively). Russell *et al.* randomized 37 PCa patients, who underwent ADT by GnRH analogs, to 0.9 or 1.8 mg E2 gel per day or matching placebo (43). After 28 days, type 1 collagen C-telopeptide (CTX1) levels were significantly decreased in the combined tE2 groups compared to placebo ($P < 0.001$).

In a nested BMD substudy of the tE2 PATCH trial, 74 men with locally advanced or metastatic PCa were randomized to ADT with LHRH agonists or tE2. Three or four patches each releasing 100 μg E2 per day were applied twice weekly to suppress testosterone to levels ≤ 1.7 nmol/L (20). The primary outcome of this substudy was the change in lumbar spine (LS) BMD at 1 year from baseline, based

on dual-energy X-ray absorptiometry. The mean 1-year change in LS BMD was -0.021 g/cm³ for LHRH agonists and $+0.069$ g/cm³ for tE2. The estimated difference between the arms was 6.7% (95% CI, 3.7; 9.7) in favor of tE2 ($P < 0.001$). Similar differences were found for the right hip (3.8%; $P = 0.003$), the left hip (4.3%; $P = 0.002$) and whole-body bone measurements (2.5%; $P = 0.002$) (Fig. 1). At 2 years, the differences were more pronounced, as shown for LS BMD (8.1%; $P = 0.001$) (20). Fractures were not reported in this relatively small substudy but were mentioned by the authors to be expected to occur in line with the known inverse relationship between fractures and BMD.

Interim reporting on quality-of-life data of 727 PCa patients included in the PATCH program provided no information on bone health but demonstrated general improvement of physical function in favor of tE2 monotherapy versus LHRH agonists ($P = 0.001$) (44). Long-term data obtained in 1694 men after a median follow-up of 3.9 years in the complete PATCH trial program revealed no difference in CV mortality or morbidity between tE2 and LHRHa, confirming the CV safety of the transdermal E2 patch by avoiding the oral first-pass hepatic metabolism of estradiol (45).

Diethylstilbestrol

There is still debate on the CV safety of DES, even at low doses, thus preventing its use as first-line treatment in PCa patients (46). In a study of over 200 men with CRPCa, 1–3 mg DES was administered together with 75 mg acetylsalicylic acid (ASA). Of the PCa patients with bone pain, 18% reported an improvement, but in 9.9% of all patients, thromboembolic complications were observed (47).

Reis *et al.* considered low-dose DES (1 mg/day) a safe treatment of hot flushes and also stated that there is limited information on its benefits for bone health. A decrease in bone resorption markers and osteoporotic fractures has been reported incidentally (22).

Ethinylestradiol

Sciarra *et al.* treated 116 patients with CRPCa with oral EE as monotherapy ADT at a daily dose of 1 mg, together with 100 mg/day ASA as anticoagulant. The median duration of treatment was 15.9 months (range, 8–36), with a median follow-up of 28 months (range, 13–36) (23). No information on bone health was provided. Cardiac failure was observed in 7.1% of the population and venous thromboembolism (VTE) in 27.7%, which is

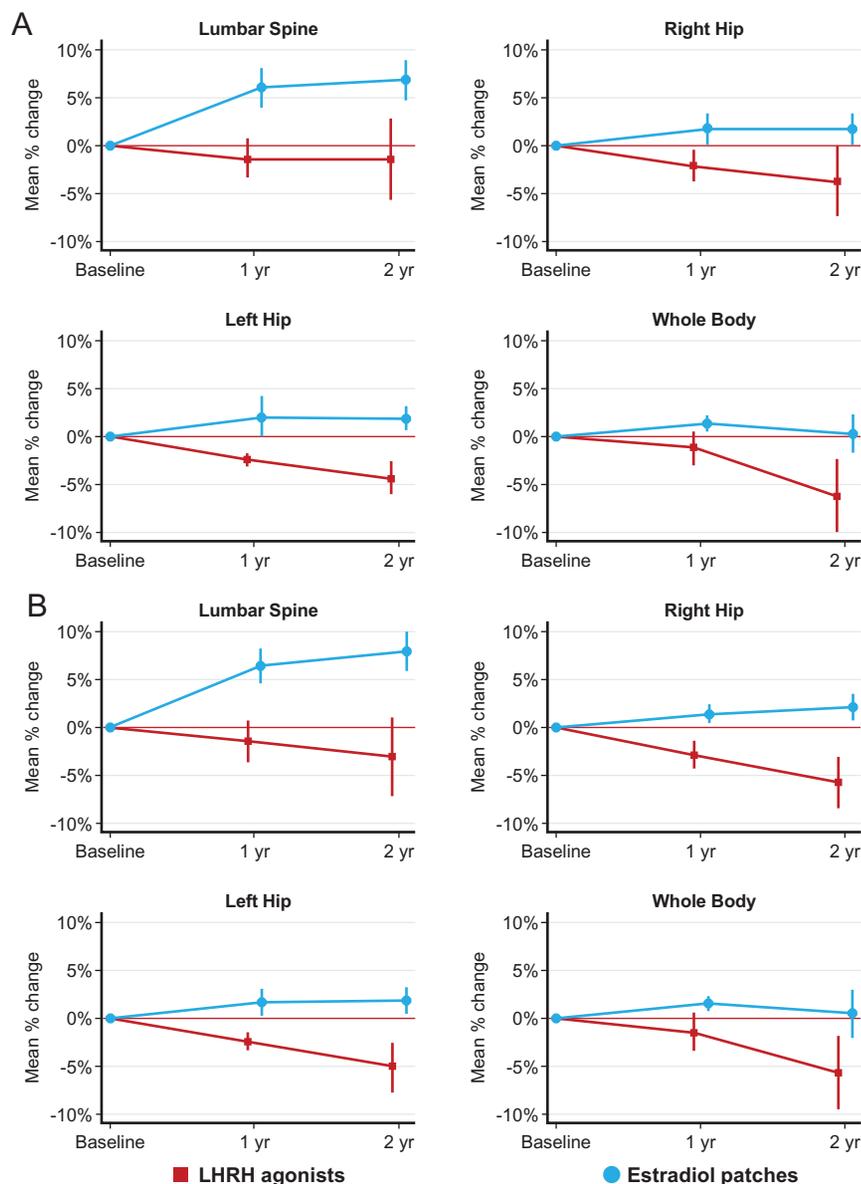


Figure 1 Mean percentage change (95% CI) in bone mineral density at 1 and 2 years from baseline by treatment arms. (A) All patients and (B) patients still on allocated treatment only (i.e. patients who were still on allocated treatment at the time of the scan with no additional anticancer therapy, with those on estradiol patch with estradiol values <250 pmol/L assumed not to be adhering to the patching regimen). Data from Langley *et al.* (2016) (20). LHRH, luteinizing hormone-releasing hormone.

not surprising in view of the very high dose of EE used. In comparison, in women, oral contraceptives contain 20–30 µg (0.02–0.03 mg) EE, a dose 40× lower than the dose used in the CRPCa patients and already implicated in an increased risk of VTE. Bone health outcome was not reported in a study using the same very high dose of 0.5–1.5 mg EE per day by Nakano *et al* (48). A lower but still high daily dose of 0.15 mg EE was used with the anticoagulant ASA and was considered to be safe, and also in this study, no bone data were provided (49). Combined therapy of 1.5 mg EE and 100 mg ASA per day was used as a re-challenge in 20 PCa patients with progression of the disease (50). No adverse CV events were reported and no information on bone health was provided. The use of ASA

in these EE studies is expected to affect arterial thrombotic events but may not have influenced the risk of VTE.

High-dose estetrol

Estetrol (E4) is a natural human estrogen, produced by the fetal liver during pregnancy only (51, 52). The structure of E4 differs from the other natural estrogens such as estrone (E1), estradiol (E2) and estriol (E3), by an additional alpha-hydroxy (OH) group at position 15 of the molecule (Fig. 2). In contrast to other estrogens, E4 does not bind to SHBG and has no active metabolites in human hepatocytes (53, 54). The activity of cytochrome P-450 is not inhibited by E4, whereas E2

and also the synthetic estrogen EE interfere with liver CYP P-450 enzymes. Thereby, E2 and EE interact with liver function and with other drugs used in PCa patients (55), such as enzalutamide, a CYP344 inducer, and are primarily eliminated by hepatic metabolism by CYP3A4 and CYP2C8. This raises concerns about drug–drug interactions compared with competing compounds such as abiraterone acetate (56).

Preclinical studies in estrogen-depleted ovariectomized mice revealed restoration of bone mineral density with E4 (57), which was confirmed clinically in postmenopausal women (24). In this phase II study, investigating daily oral doses of 10–40 mg E4 for 28 days, CTX1 levels decreased by 35–46%, and osteocalcin decreased by 10%. Clinical studies in women have shown that E4 mimics most of the beneficial effects of E2, including reduction of bone turnover and stabilization of bone metabolism, and may even be superior to E2 by a lower risk of CV events since E4 has less impact on hemostasis, on both coagulation and fibrinolysis (24, 54, 58).

A dose-finding study in healthy men resulted in the selection of a dose of 40 mg E4 for further development in the treatment of advanced PCa (59). This relatively high dose of estetrol (HDE4) has been investigated as a co-treatment of ADT with LHRHa in a 24-week, phase II, placebo-controlled study in 62 patients with advanced PCa, aiming primarily at the prevention of estrogen-deficiency signs and symptoms including bone loss and secondly, at additional anti-tumor effects (the PCombi study) (25). Bone metabolism markers increased in the LHRHa/placebo group by 48% for osteocalcin and 151% for CTX1 at 24 weeks. In the HDE4 co-treatment group,

osteocalcin levels decreased by 22% ($P < 0.0001$) and CTX1 levels by 25% ($P < 0.0001$) at 24 weeks compared to baseline, confirming complete protection against bone loss by this dose of E4 (Fig. 3 and Table 2).

Discussion

ADT in advanced PCa with GnRH analogs causes bone loss and an increased risk of fractures. The intention of this review is to summarize the current knowledge of co-treatment with estrogens, as alternative to existing BSAs, to prevent these problems. The purpose of ADT is to maximally suppress the levels of testosterone, the primary and most important PCa tumor growth stimulator (7). Since testosterone is the biochemical precursor of E2, many unwanted effects of ADT are due to the concomitant loss of E2 when testosterone is suppressed. In general, urologists and oncologists involved in the treatment of advanced PCa tend to underestimate the clinical importance of the loss of E2, which causes more problems than the loss of testosterone (see Table 1). Furthermore, in the past, the estrogens used for the treatment of advanced PCa were very effective anti-tumor agents but were replaced by GnRH analogs for safety reasons. The new options of transdermal E2 and oral E4 are safer than the old estrogens such as DHEA, EE and oral E2 and retain the anti-tumor effects of estrogens (20, 25, 45). Estradiol levels in healthy men are low in the range of 10–50 pg/mL and are comparable to those in women after menopause. During GnRH analog ADT treatment, with both LHRH agonists and GnRH antagonists, E2 levels are decreased by up to 80% (19, 25). One of the most important consequences of the loss of E2 by ADT is the increase of bone turnover with a stronger increase of bone resorption than bone formation, resulting in bone loss, osteoporosis and fractures (7, 21). Therefore, the use of estrogens to mitigate these negative effects appears attractive. However, estrogens have a negative reputation with respect to CV side effects, in particular, VTE. Especially, the synthetic estrogens, DES and EE, have a negative reputation and track record (23, 47), while parenteral E2 resulted in an increase in non-fatal CV events (40). It is not the intention of this review to judge the validity of these concerns, but to review the value of two new estrogen therapy options, tE2 and oral HDE4, that present with better CV safety, and have emerged as potential alternative BSAs.

At present, guidelines for ADT advise to combine this treatment in selective cases with specific BSAs such as bisphosphonates, denosumab or SERMs (13). Similarly to their concomitant use in breast cancer patients (60), all

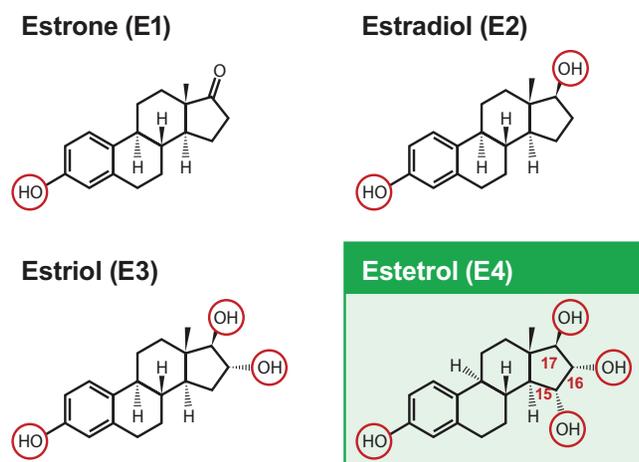


Figure 2
The molecular structures of the four natural estrogens.

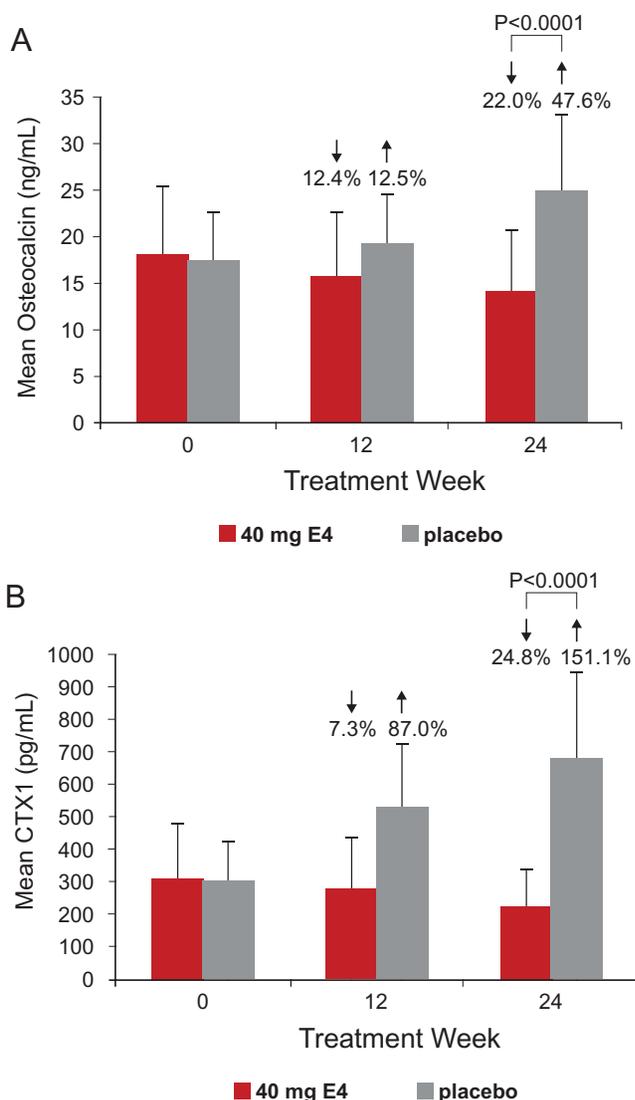


Figure 3 Mean levels of bone turnover markers (osteocalcin (A), CTX1 (B)), after 12 and 24 weeks of treatment with 40 mg estrol (E4) or placebo in patients with prostate cancer treated with an LHRH agonist. Data from Coelingh Bennink *et al.* (2021) (25). CTX-1, type I collagen telopeptide.

three classes of BSAs are effective in preserving bone in PCa patients, although SERMs may be less potent. Major problems related to ADT co-treatment with BSAs are the side effects, which can be summarized as follows. Prescribing information of adverse events on bisphosphonates refers to muscle and bone pain and gastrointestinal disorders, and those of denosumab are pain in the extremities and musculoskeletal pain. Hypocalcemia may also occur. A disadvantage of denosumab and some SERMs is its inconvenient parenteral administration. Compared to bisphosphonates and denosumab, SERMs seem to be less effective in preserving bone mass in the PCa population,

Table 2 Bone turnover (percentage change from baseline) after 24 weeks of treatment with 40 mg estrol or placebo daily co-administration in patients with prostate cancer treated with an LHRH agonist (25). Results are reported as mean (s.d.).

Laboratory parameter	Percentage change from baseline		p ^a
	40 mg E4 (n=37)	Placebo (n=20)	
Osteocalcin (ng/mL)	-22.0 (19.7)	+47.6 (47.2)	<0.0001
CTX1 (ng/mL)	-24.8 (34.6)	+151.1 (109.1)	<0.0001

^aKruskal-Wallis test comparing week 24 laboratory levels of 40 mg estrol (E4) to placebo.

although BMD may not fully reflect the fracture risk (13, 61, 62). In PCa patients, gastrointestinal and cardiovascular problems are the most important adverse events of SERMs (16).

In view of the side effects of conventional BSAs and the promising data for tE2 and oral E4, a revision of the use of these estrogens as BSAs for ADT co-treatment seems worthwhile. Both tE2 and E4 are given at rather high dosages. Three to four patches releasing 100 µg E2 each per 24 h replaced twice weekly were used in the PATCH trial (20, 45). Oral use of E4 has been investigated in PCa patients based on earlier dose-finding studies at a high dose level of 40 mg E4 (HDE4) per day (25), which is more than double the 15 mg daily dose developed for hormonal oral contraception and menopausal hormone therapy (63, 64, 65). Major differences between both methods are that tE2 is used as primary ADT to suppress testosterone with as additional benefit the replacement of E2 (20, 45), whereas the objective of HDE4 is to act as a co-treatment of GnRH analogs and have a dual efficacy by combining anti-tumor effects and estrogen replacement (25). Not only do the objectives of the treatments differ but also the route of administration is different. The tE2 is given via a patch to avoid the low 5% oral bioavailability of E2 and the unwanted effects of oral E2 on liver function, especially on hemostasis with its concomitant increased risk of VTE (45). Oral HDE4 has a bioavailability of 70–80% and this natural fetal estrogen has been shown to have little effect on liver function and hemostasis and is expected to carry a lower risk of VTE compared to E2, as well as to other estrogens used in the past for ADT (24, 54, 57, 58). The choice between tE2 and oral HDE4 as far as the route of administration is concerned and is therefore a matter of patient acceptability. When comparing the efficacy of tE2 and HDE4, the testosterone suppression objective has been met with the dose of tE2 used. Oral HDE4 has been shown to support the initial testosterone suppression, thereby preventing the initial testosterone rise (the

testosterone flare') in case LHRH agonists are used for ADT. Another advantage of HDE4 is the significant increase in the suppression of biologically active free testosterone levels by increasing the levels of SHBG, which is a specific effect of the oral route of administration of estrogens (25). Since, at present, no head-to-head studies of tE2 vs HDE4 are available, it is difficult to compare the efficacy of tE2 monotherapy vs co-treatment of a GnRH analog with HDE4, but the separate studies suggest that suppression of total as well as free testosterone may be better with the HDE4 co-treatment approach (20, 25).

The number of patients treated with tE2 and LHRHa/HDE4 in studies measuring bone parameters is comparable in both studies published (respectively 27 and 37 patients), and both tE2 monotherapy and LHRHa/HDE4 co-treatment seem to completely prevent deterioration of bone metabolism at the dose levels used. The PCombi HDE4 study generated significant data on a strong bone protective estrogenic effect of HDE4, with no effect or even a decrease of bone turnover with HDE4/ADT co-treatment, compared to a strong increase of bone metabolism with LHRH agonists only (25). Treatment with tE2 for up to 2 years resulted in a significant improvement in BMD compared to LHRHa (20). This confirms the prevention of bone loss and the potential to decrease the risk of fractures of tE2, although fractures were not mentioned in the PATCH bone sub-study. So far, no BMD and fracture data are available for LHRHa/HDE4, since the phase II HDE4 study lasted for only 24 weeks and the bone results of LHRHa/HDE4 are based on biochemical bone metabolism data only (25).

When comparing tE2 and HDE4, also the effect on other signs and symptoms of testosterone loss and estrogen deficiency due to ADT and adverse events in general is relevant (Table 1). In the large comparative phase III PATCH trial program, comparing 904 PCa patients treated with tE2 and 790 with LHRHa for a median follow-up of 3.9 years, fatal CV events occurred in 1.2 and 1.9%, respectively (45). Long-term data on CV safety of the LHRHa/HDE4 co-treatment are not yet available. The most frequent adverse events in the quality-of-life (QoL) part of the PATCH study were gynecomastia with tE2 (86% vs 38%) and hot flushes with LHRHa (86% vs 35%) (44). In the shorter (24 weeks) and smaller PCombi study (41 patients with LHRHa/ HDE4 co-treatment and 21 patients with LHRHa/placebo), daily hot flushes occurred in 6% and 55%, respectively, and gynecomastia was reported in 17% of HDE4 co-treated patients (25). More detailed information on the QoL of the LHRHa/HDE4 co-treatment is needed. Gilbert *et al.*

suggest to investigate, in the future, tE2 in addition to LHRHa as a treatment for hot flushes (44), which would be a co-treatment comparable to HDE4 in PCombi, and alternatively, also HDE4 only could be investigated as monotherapy for ADT.

Based on the available information, both tE2 and HDE4 seem to be effective in prevention/treatment of estrogenic side effects of ADT, including the normalization of bone metabolism. In conclusion, since the BSAs only prevent bone loss, may have serious side effects and have no effect on the other symptoms caused by the loss of estrogens due to ADT, estrogen therapy with tE2 or HDE4 may become an alternative treatment option to avoid the interference of ADT with bone metabolism. Confirmation of the beneficial effects on bone health in patients with advanced PCa is needed, with special emphasis on bone mass and fracture rate.

Declaration of interest

H J T C B is president and a shareholder of Pantarhei Oncology (PRO), an affiliate of Pantarhei Bioscience BV. J K is chief medical officer and shareholder of PRO, Y Z is a former employee and shareholder of PRO and I J S is R&D Director and shareholder of PRO. D M S is member of advisory boards of Astellas, Janssen and Bayer and received research grants from Astellas and Besins. N W C received grants and fees from Janssen, AstraZeneca, Astellas and Bayer. R J A v M is member of the advisory board of PRO and received grants and fees from Astellas, Ipsen, Astra Zeneca, Bayer and Janssen. F M J D is paid consultant for PRO and member of the advisory board of PRO. The other authors declare no conflict of interest.

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