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Osteoporosis and Fracture Risk in Men with Prostate Cancer

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Bone health is important in men with prostate cancer (PCa). Age is the most influential risk factor for fragility fractures, and PCa occurs predominantly in older men. Sex hormones are important determinants of bone mineral density (BMD), which is a risk factor for fracture, and treatment for many men with PCa includes induction of hypogonadism. Unsurprisingly, rates of bone loss in men with PCa treated with androgen deprivation therapy (ADT) are accelerated. In community-dwelling older men, hip BMD declines by approximately 2% over 4.6 yr of observation [1]: In men with PCa receiving ADT, the same loss occurs over 1–2 yr [2,3]. The important clinical outcome is fracture. Data from a large observational study suggest that ADT might increase the relative risk of any fracture by approximately 50% during 5–10 yr of follow-up [4].

In this month’s issue of *European Urology*, Langley et al report the findings of a BMD substudy of the Prostate Adenocarcinoma Transcutaneous Hormones (PATCH) trial, an open-label randomised comparison of the effects of luteinising hormone-releasing hormone (LHRH) agonist therapy with transdermal oestradiol on overall and progression-free survival in men with locally advanced or metastatic PCa [5]. Over 2 yr, BMD at spine and hip was 6–8% higher in the men randomised to oestradiol than in those allocated to LHRH agonists. Both treatments induce profound androgen deficiency, but only LHRH agonists decrease serum oestradiol levels. To those unfamiliar with metabolic bone disease, the finding that treatment with oestradiol preserves BMD in men might be puzzling. However, experiments of nature and carefully designed trials in healthy older men have established that oestrogen is an important regulator of male bone health [6], acting to restrain bone resorption and to maintain BMD.

The findings of Langley et al are consistent with existing evidence: they also suggest the possibility that ADT using transdermal oestradiol rather than LHRH agonists might avoid the adverse skeletal effects of the latter. However, it is premature to infer clinical superiority of transdermal oestradiol. BMD is only a surrogate for the important clinical outcome of fracture, and extrapolating from surrogate end points to clinically important outcomes is unwise. Fracture data are being collected in the parent PATCH trial and will be pivotal to the conclusions drawn about the relative effects of the interventions for bone health in men with PCa. In addition, bone health will be only one component of the overall balance of benefits and risks of transdermal oestradiol and LHRH agonists that will emerge from the PATCH trial. In fact, fracture might be a relatively unimportant consideration in the final equation because of its infrequency. Another adverse effect of particular interest during ADT, cardiovascular events, occurred in 9% of participants in PATCH over only 18 mo [7]. Fractures might occur substantially less often. At baseline, participants in PATCH had robust BMD and low prevalence of clinical risk factors for fracture. In a typical PATCH participant, the estimated absolute risks of major osteoporotic fracture (hip, clinical spine, forearm, shoulder) and of any fracture are only 4.1% and 12%, respectively, over 10 yr (FRAX World Health Organisation Fracture Risk Assessment Tool, [https://www.shef.ac.uk/FRAX/tool.jsp](https://www.shef.ac.uk/FRAX/tool.jsp); Garvan Institute bone fracture risk calculator, [http://www.garvan.org.au/bone-fracture-risk](http://www.garvan.org.au/bone-fracture-risk)). In the placebo group of a clinical trial that enrolled a population of men of similar age to that in PATCH but was enriched for men with low BMD and/or prevalent fracture, only 7.2% experienced a fracture over 3 yr [3].
Until further results become available, including fracture data from PATCH, how should clinicians manage the bone health of men with PCa? A good starting point is to estimate the patient’s absolute fracture risk, which is possible using clinical information and, if available, BMD measurement. The available risk algorithms differ in the input variables, sites of fractures included, horizons of fracture prediction reported, and approaches to the incorporation of competing risk of death. Each can be used without BMD measurement [8]. In elderly men, use of a calculator that estimates fracture risk over a short but clinically relevant interval (3–5 yr) may be preferable to one that uses a longer prediction interval [8]. Men estimated to be at moderate or high risk of fracture during ADT can be considered for treatment with an antiresorptive agent such as a bisphosphonate or denosumab. In osteoporotic populations, each of these agents reduces the relative risk of clinical fractures by approximately 33% [9]. In men with PCa, each agent improves BMD, and denosumab may reduce fracture risk [2,3]. For men estimated to be at low risk of fracture during ADT, no specific intervention is required, but review of fracture risk is sensible after 3–5 yr, depending on clinical circumstances. Increasing calcium intake and/or taking vitamin D supplements are ineffective treatments for reducing fracture risk in older community-dwelling adults [10] and cannot be justified in men with PCa.

Conflicts of interest: Andrew Grey is a shareholder in Auckland Bone Density, a company that provides bone density measurements.

References