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TREATMENT-INDUCED BONE LOSS IN PROSTATE CANCER PATIENTS: AN INSIGHT INTO THE GONADAL CONTROL OF BONE REMODELLING

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Abstract

Prostate cancer is diagnosed in over 1.5 million new patients every year, with many of them requiring prolonged treatment, which – particularly in advanced cases – involves androgen deprivation therapy with the use of luteinizing hormone-releasing hormone analogues. Amongst several side-effects resulting from dysregulation of the body's hormonal control, skeletal changes have been associated with the greatest patient burden. The skeletal system is a highly specialised component of the human body that is tightly regulated by local and systemic factors. While the mechanism of bone remodelling has been described in detail by previous studies, the complex mechanism of its control still remains to be fully elucidated. In this work, the authors aimed to conduct a systematic review of the existing literature in an effort to synthesise the existing knowledge about the biochemical pathways involved in the control of bone remodelling. This has been subsequently utilised to discuss the mechanisms by which gonadal hormones (oestrogens and androgens) influence bone physiology, with regards to both established theories and emerging hypotheses. The scientific findings summarise in the review might aid physicians in understanding the mechanism of androgen-deprivation-therapy-related bone loss and identifying the most effective treatment regime. Whilst there currently seems to be a lack of scientific consensus on the precise aetiology of these pathological changes, further explorations into the intricate properties of the human bone might yield exciting discoveries that could contribute to the development of new clinical solutions for prostate cancer patients in the future.

Keywords: prostate cancer, androgen-deprivation therapy, bone loss, bone remodelling

Abbreviations

ADT – androgen deprivation therapy; BMD – bone mineral density; ERα – oestrogen receptor alpha; IGF-2 – insulin-like growth factor 2; IL-1R – interleukin 1 receptor; IL-6 – interleukin 6; LHRH – luteinizing hormone-releasing hormone analogues; M-CSF – macrophage colony stimulating factor; OPG – osteoprotegerin; PGE2 – prostaglandin E2; RANK – receptor activator of nuclear factor-kappa B; RANKL – ligand for the receptor activator of nuclear factor-kappa B; SERMs – selective oestrogen receptor modulators; TGF-β – transforming growth factor β

Introduction

The skeletal system is a highly specialised component of the human body which enables locomotion, provides protection to major organs, and acts as a structural framework for interaction with the environment. Because of the fundamental importance of these properties for functioning of the human organism, the skeleton undergoes constant, tightly regulated processes of adaptation and repair, collectively referred to as 'bone remodelling'. This work will aim to provide a comprehensive overview of the biochemical mechanisms underpinning these structural changes, which will then serve as a theoretical foundation for an exploration of the influence of androgens and oestrogen on bone metabolism. The exact extent to which systemic hormones affect bone remodelling will be elucidated by conducting a literature-based analysis of the pathogenesis of bone diseases in prostate cancer patients with treatment-induced hypogonadism. Finally, the aspects of bone physiology considered throughout the essay will be applied to evaluate both conventional and novel therapies available to this population of patients.

Mechanism of Bone Remodelling

When the uniquely diverse roles of the human skeleton are considered in a collective manner, there appears to be an evolutionary need for a mechanism that would allow to actively adjust the balance between the bone's physical resistance and its motion-aiding lightness. This has been addressed by bone remodelling, which provides the skeletal system with an ability to remove and replace osseous tissue in response to mechanical stress or microscopic injuries. By doing so, the bone maintains its structural integrity whilst also permitting a degree of phenotypic plasticity in the face of changing environmental requirements.

At its most fundamental level, the process of bone remodelling is orchestrated by osteocytes, which are able to detect changes within osseous tissue via a complex network of actin-containing dendritic connections. When the bone is subjected to mechanical loading, the arrangement of actin fibres becomes disrupted, resulting in an opening of mechanosensitive calcium channels on the surface of osteocytes (*Qin et al.*, 2020). The consequent influx of ions stimulates osteocytes to release prostaglandin E2 (PGE2), which acts to increase the population of osteoblasts at the region of bone tissue where remodelling is required (*Feyen et al.*, 1985). The osteoblasts, in turn, secrete macrophage colony stimulating factor (M-CSF), promoting proliferation of osteoclast precursors that join osteoblasts to form a basic multicellular unit. These progenitor cells subsequently begin expression of receptor activator of nuclear factor-kappa B (RANK), which – upon stimulation by an osteoblast-derived ligand (RANKL) – mediates their differentiation into active osteoclasts.

Having adopted a mature phenotype, osteoclasts commence the process of bone resorption by synthesising hydrochloric acid and proteolytic enzymes, such as matrix metalloproteinases or cathepsin K (*Delaissé et al.*, 2003). These biochemical factors act to degrade hydroxyapatite crystals and collagen matrix, leading to a localised removal of osseous tissue. As the resorption progresses, the activity of osteoclasts starts to be negatively regulated by osteoprotegerin (OPG), which is released from osteoblasts to bind and thereby inhibit the actions of free ligand for the receptor activator of nuclear factor B (RANKL) molecules. Due to a decrease in RANKL-mediated stimulatory signals, osteoclasts undergo apoptosis, which prevents further, unwanted bone resorption.

The external fragments of collagenous matrix – exposed by osteoclasts – attract endocytic receptors of 'reversal cells' that act to phagocytose the remaining collagen fibres (*Abdelgawad et al.*, 2016). This prepares the remodelled portion of the bone for attachment of osteoblasts, which subsequently utilise their extensive rough endoplasmic reticulum to replace the resorbed tissue with newly synthesised osteoid. Then, under what is hypothesised to be an osteocyte-mediated regulation, the premature bone matrix becomes fortified with hydroxyapatite crystals (*Atkins* and *Findlay*, 2012). In consequence, osteoblasts become enclosed within a mineralised bone tissue, which causes them to commit apoptosis or differentiate into osteocytes that can initiate another cycle of bone remodelling in the future.

When the process of bone remodelling is approached from a broader perspective, it can be observed that the RANKL:OPG ratio plays a crucial role in controlling the degree of bone resorption and formation. Hence, alterations to the relative proportions of both molecules can allow for localised changes in bone structure – it is through this mechanism that the skeletal system responds to mechanical stimuli and systemic factors, such as cytokines or gonadal hormones.

Influence of Sex Hormones on Bone Remodelling

Androgen-mediated effects

Since the first suggestion of their involvement in skeletal homeostasis in 1948, androgens have been found to exert a number of important regulatory effects on the bone metabolism (*Albright* and *Reifenstein*, 1948). This unobvious connection between endocrine and skeletal systems is based on androgen receptors, whose expression has been identified in all types of bone cells (*Vanderschueren et al.*, 2004).

According to the evidence provided by *in vitro* studies, androgens display an ability to upregulate the synthesis of transforming growth factor β and insulin growth factor receptors in osteoblasts (*Kasperk et al.*, 1990; *Bodine et al.*, 1995). These molecular changes promote divisions and differentiation amongst cells of osteoblastic linage, leading to an increased deposition of bone tissue during the remodelling cycle. Whilst the recruitment of osteoblasts could result in elevated levels of osteoclast-stimulating RANKL, androgens prevent osteoclastogenesis by decreasing the local availability of interleukin-6 (*Yoshitake et al.*, 2008). Interestingly, androgens acting on osteoblasts appear to also enhance the expression of their own receptor, which increases the sensitivity of their cellular targets to further hormonal stimulation (*Wiren et al.*, 1999). This effectively creates a positive feedback loop that significantly amplifies the potential of male sex hormones to influence bone remodelling (Figure 1).

The above evidence derived from laboratory studies seems to have its reflection in human subjects as well. Clinical trials investigating the effects of testosterone therapy in elderly males with decreased testosterone levels have found that androgen supplementation resulted in an increase in Bone Mineral Density (BMD) and estimated bone strength when compared to placebo (*Ng Tang Fui et al.*, 2021; *Snyder et al.*, 2017). These anabolic effects were observed in both appendicular (tibia, radius) and axial (vertebrae, pelvis) parts of the skeleton. The improvements in BMD were also more profound in cortical than cancellous bone, which is consistent with the reported variation in concentration of androgen receptors in both types of osseous tissue (*Kasperk et al.*, 1997).

Yet, the exact extent to which androgens influence bone physiology remains rather challenging to ascertain due to a large number of their systemic effects that could act as potential confounding factors. First, androgen-induced muscle growth can subject bones to increased mechanical loading that is known to promote deposition of new osseous tissue. Some studies have also identified a stimulatory effect of testosterone on the intestinal absorption of calcium, which reduces the need for bone resorption to contribute to calcium homeostasis (*Hope et al.*,1992). Most importantly, however, androgens act as precursors for synthesis of the vast majority of male oestrogen – a hormone that itself exhibits a significant osteomodulatory potential.

Oestrogen-mediated effects

Despite being traditionally perceived as a 'female hormone', oestrogen has been found to play a major role in the maintenance of normal bone physiology in both women and men. Analogously to androgens, oestrogen exerts its influence on osseous tissues via oestrogen receptors alpha (ERα), which are situated within the cytoplasm of bone cells (*Gustafsson et al.*, 2016). Stimulation of ERα by its ligand initiates a number of biochemical

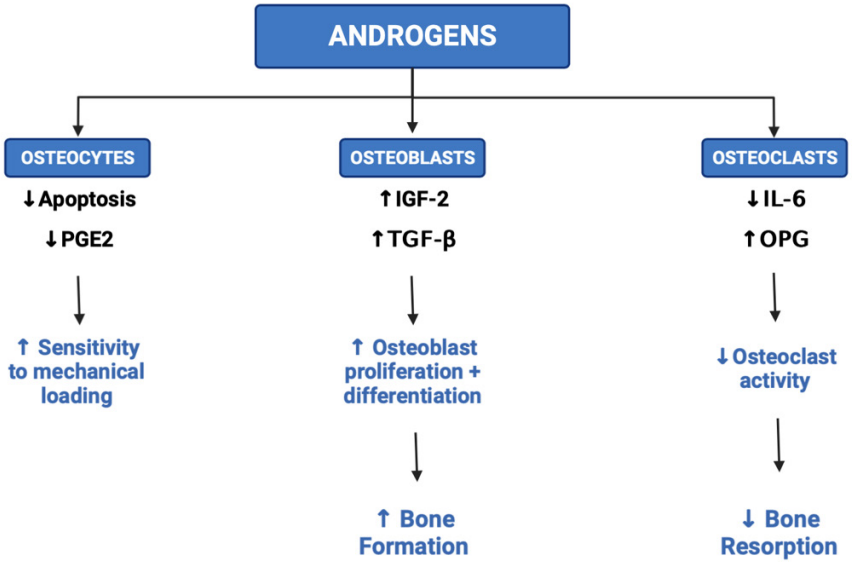

Fig. 1. A diagram summarising the physiological effects of androgens on osteocytes, osteoblasts, and osteoclasts, along with their respective consequences for bone tissue homeostasis (generated using BioRender®). IGF-2 – insulin-like growth factor 2; IL-6 – interleukin 6; OPG – osteoprotegerin; PGE2 – prostaglandin E2; TGF-β – transforming growth factor β (details in the text)

pathways, whose subsequent effects can be broadly categorised into inhibition of bone resorption and promotion of bone deposition.

The osteoprotective potential of oestrogen seems to primarily stem from its ability to downregulate the activity of osteoclasts. As evidenced by experiments involving genetically modified mice, activation of osteoclastic ER promotes the expression of Fas ligand, which is implicated in the induction of apoptosis (*Nakamura et al.*, 2007). Whilst cell death is associated with a release of pro-osteoclastogenic interleukin-1, oestrogen has also been shown to reduce the number of interleukin-1 receptors on osteoclast precursors, hence preventing their differentiation into active cell types (*Sunyer et al.*, 1999). This effect is further supported by an increased local availability of OPG, whose osteoblastic synthesis is stimulated via ER-mediated pathways (*Hofbauer et al.*, 1999). It can therefore be seen that oestrogen exerts a significant degree of inhibitory control on osteoclasts at every stage of their development.

In addition to its anticatabolic influence, oestrogen seems to also act as a catalyst for deposition of new osseous tissue. According to the results of biochemical investigations, this effect arises mainly from the ability of oestrogen to prolong the lifespan of osteoblasts and stimulate the maturation of their progenitor cells (*Bradford et al.*, 2010). The former is believed to be a consequence of a downregulated expression of proapoptotic agents, and an enhanced activity of glutathione reductase which neutralizes reactive oxygen species that could otherwise cause cell death (*Almeida et al.*, 2010). Interestingly, oestrogen has also been shown to increase the amount of PGE2 production by osteocytes, contributing to their greater sensitivity to mechanical loading (*Joldersma et al.*, 2001). Taken together, the influence of oestrogen on osteoblasts and osteocytes enables the osseous tissues to actively respond to any demands for bone formation or repair, which is essential for the maintenance of skeletal integrity (Figure 2).

In summary, androgens and oestrogen influence the bone physiology via a complex array of biochemical mechanisms. By doing so, the sex hormones provide an important regulatory control over the process of bone remodelling. This allows to prevent excessive resorption or deposition of skeletal tissues, which helps to maintain the bone mass within a physiologically normal range. Thus, any imbalances of hormonal signalling are likely to disrupt this homeostatic equilibrium and lead to development of bone pathologies.

Male Hypogonadism and Bone Remodelling

Skeletal Effects of Prostate Cancer Treatment

With over 52 000 new cases diagnosed each year, prostate cancer is the second leading cause of malignancy-related death amongst United Kingdom (UK) men (*Cancer Research UK*, 2015). According to the current scientific understanding, prostate cancer cells – prior to developing a hormone-resistant phenotype in advanced stages – are highly dependent on androgen-mediated stimulation for

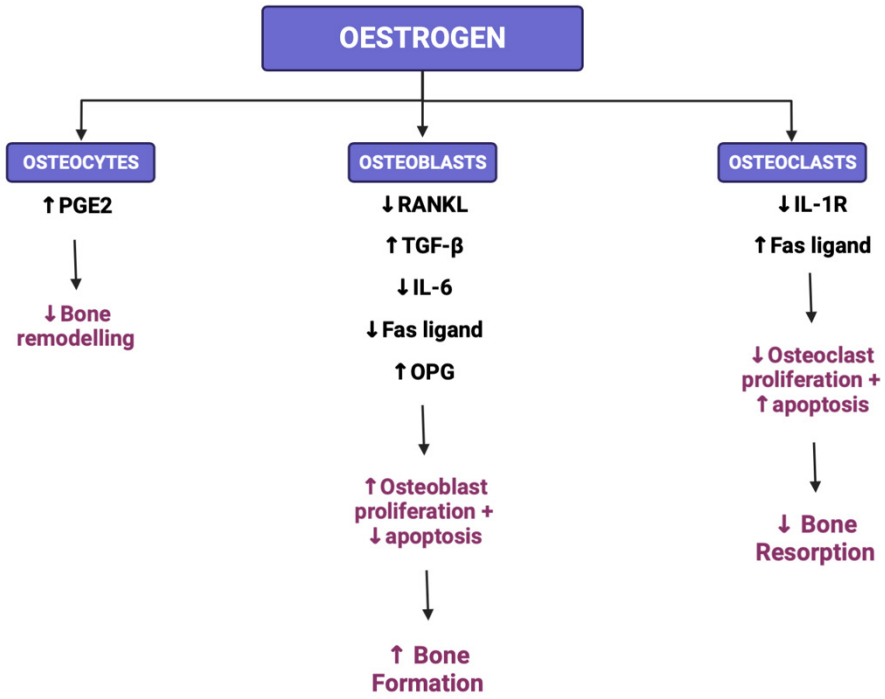

Fig. 2. A diagram summarising the physiological effects of oestrogen on osteocytes, osteoblasts, and osteoclasts, along with their respective consequences for bone tissue homeostasis (generated using BioRender®). IGF-2 – insulin-like growth factor 2; IL-1R – interleukin 1 receptor; IL-6 – interleukin 6; OPG – osteoprotegerin; PGE2 – prostaglandin E2; RANKL – ligand for the receptor activator of nuclear factor-kappa B; TGF-β – transforming growth factor β (details in the text)

their survival and progression (*Tan et al.*, 2014). In line with these observations, the initial treatment offered to prostate cancer patients focuses on inducing a state of androgen deprivation using synthetic luteinizing hormone-releasing hormone analogues (LHRH), such as leuprolide. Whilst this approach might initially seem counterproductive, continuous LHRH therapy results in a downregulated expression of LHRH receptors on the surface of gonadotrophs in the anterior pituitary (*Limonta et al.*, 2001). This leads to a reduced secretion of luteinizing and follicle-stimulating hormones, which in turn limits the production of androgens and oestrogen. However, due the fundamental importance of sex hormones for the control of bone remodelling, treatment-induced hypogonadism in prostate cancer patients is frequently associated with adverse skeletal effects.

According to the evidence from histomorphometric investigations, the initiation of androgen deprivation therapy (ADT) has a number of implications for the function of bone cells. More specifically, treatment-induced hypogonadism has been found to promote osteoclast activity, whilst also inhibiting the signalling pathways responsible for the recruitment of osteoblasts (*Jackson et al.*, 1987; *Wang et al.*, 2021). In consequence, the skeletal tissues of prostate cancer patients experience an excessive amount of bone resorption, which contributes to a decrease in BMD. When this pathological mechanism was investigated in a longitudinal study, ADT was observed to cause reductions of BMD at multiple skeletal sites that ranged between 2.4–4.0% per year (*Greenspal et al.*, 2005). The adverse effects of ADT seem to continue throughout the entire duration of the therapy, with the most profound changes occurring in the first year of treatment (*Kiratli et al.*, 2001). The loss of osseous tissue, which primarily affects the trabecular compartment, leads to a reduction in the compressive bone strength that is likely to predispose hypogonadal patients to fractures. Indeed, an analysis of over fifty thousand cases of prostate cancer showed that ADT contributed to an increased risk of fractures, with the incidence rising along with the number of administered LHRH doses (*Shahinian et al.*, 2005).

Due to the significant burden associated with this method of prostate cancer treatment, some of the more recent studies have proposed to replace LHRH analogues with selective androgen receptor antagonists (*Nyquist et al.*, 2021). However, the question remains which sex hormone is primarily responsible for the observed reductions in BMD, and whether supplementation of one of them would be sufficient to compensate for the inhibition of the other.

Androgens or Oestrogen?

When attempting to dissect the individual contributions of androgens and oestrogen to the process of hypogonadal bone loss in male populations, there appears to be a substantial degree of scientific discrepancy. According to a study conducted on a cohort of Swedish patients, low levels of both testosterone and oestrogen were found to correlate with reductions in BMD and increased fracture risk (*Mellström et al.*, 2006). This stands in marked contrast to the findings of an earlier investigation, which identified such association only for decreased levels of oestrogen (*Szulc et al.*, 2003). To further complicate the picture, an Australian observational study reached a conclusion that low testosterone – and not oestrogen – is associated with an increased incidence of fractures (*Meier et al.*, 2008).

The inconsistent results seen across the literature are likely to stem from the considerable number of confounding factors associated with the investigations of gonadal influences on bone. For instance, the study by Szulc et al. did not supplement their analysis with data on calcium intake, which is an important factor involved in maintenance of bone homeostasis. The remaining two studies, on the other hand, failed to consider the participants' consumption of alcohol, a known inhibitor of osteoblastic activity (*Laitinen* and *Välimäki*, 1991). Such investigations can be even more challenging to conduct among prostate cancer patients as skeletal metastases or exposure to radiation can significantly influence the bone physiology.

Therefore, the scientific community remains in a considerable need of a greater number of multivariate analyses that could advance the current understanding of skeletal disorders related to male hypogonadism. The new insights could then allow for identification of the safest and most effective method of administering ADT, which would contribute to a better quality of life amongst prostate cancer patients undergoing treatment.

Prevention of ADT-related Skeletal Complications

Whilst a substantial body of evidence exists showing the commencement of ADT to contribute to a reduction in BMD, along with several pathological states that can develop in consequence, the most effective treatment approach aimed at prevention of these skeletal complications still remains to be elucidated (*Alibhai et al.*, 2018). Considering the shared aetiology of pathological changes in ADT-associated side effects and age-related osteoporosis, current scientific efforts have focused on the assessment of the efficacy of bisphosphonates, selective oestrogen receptor modulators (SERMs) and denosumab in prostate cancer patients undergoing ADT. From a molecular perspective, bisphosphonates and SERMs exert an osteoprotective effect by stimulating an increased apoptosis of osteoclasts and hence preventing bone resorption (*Hussain et al.*, 2020; *Langdahl et al.*, 2020). Denosumab, on the other hand, prevents activation of RANKL by acting as a competitive inhibitor of osteoblast-derived RANK (*Hussain et al.*, 2020).

According to the results of a recent meta-analysis, bisphosphonates lead to a statistically significant improvement in bone mass at all of the investigated skeletal sites

(total hip, femoral neck and lumbar spine), with the mean percentage difference being equal to 7.1% (*Joseph et al.*, 2019). Interestingly, the changes observed in the studies were similar in patients who received bisphosphonates orally and those who received them intravenously. The analysis concluded that prostate cancer patients undergoing ADT responded best to therapy that included risedronate (average change in skeletal mass = 12.7%) (*Choo et al.*, 2013). The results, however, showed significant inconsistencies between skeletal sites – risendronate proved to be the most effective at spinal sites, but hip and femoral locations responded best to zoledronic acid and alendronate respectively (Table 1). Moreover, approximations for risendronate were associated with large confidence intervals (CI = 0.57–24.83%), making the validity of the findings questionable (*Joseph et al.*, 2019). While bisphosphonates delivered orally can be more convenient for the patients, the choice of the most effective bisphosphonate may rely on the site where a skeletal pathology has been identified but remains in need of further investigations.

Studies exploring the effects of SERMs in the population of prostate cancer patients undergoing ADT revealed statistically significant improvements in BMD at all skeletal sites investigated. Overall, the effect size was smaller than that seen in trials involving bisphosphonates. Amongst the two SERM drugs (raloxifene and toremifene) evaluated in the study, raloxifene was found to lead to a slightly higher percentage increase in BMD (range = 2.0–3.7%) in comparison to toremifene (range = 1.9–2.3%) (*Joseph et al.*, 2019). The greatest percentage improvement was seen in lumbar vertebrae (raloxifene = 2%; toeremifene =2.3%, with the effect being significantly less prominent than one seen in case of bisphosphonates (*Smith et al.*, 2004, 2011) (Table 1). Given that similar rates of adverse effects have been reported in the scientific literature for both therapeutic agents – which involved osteonecrosis of the jaw and hypocalcaemia – bisphosphonates can be considered a better pharmacological option due to their superior effectiveness (*Gartrell et al.*, 2014).

A more novel therapeutic agent – denosumab – is a monoclonal antibody designed to bind to RANKL, hence inhibiting activation and differentiation of osteoclasts during the process of bone remodelling. The reported clinical effectiveness of denosumab (lumbar spine = 7.1%; hip = 3.2%; femoral neck = 3.9%) is similar to that of bisphosphonates (lumbar spine = 6.7%; hip = 4.8%; femoral neck = 3.9%), but recent systematic reviews suggest the novel agent to be associated with higher patient adherence and a decreased risk of fractures. Additionally, the data from the clinical trials involving the monoclonal antibody showed a smaller degree of uncertainty, contributing to a higher level of statistical significance. Thus, denosumab could be a highly effective therapeutic agent in prostate cancer patients undergoing ADT – however, as in case of other newly developed pharmacological options, further investigations are required to identify the best treatment regime that would allow physicians to maximise clinical outcomes and quality of life amongst prostate cancer patients suffering from ADT-related bone mass loss.

The above evidence has already been partly translated to clinical guidelines that are currently available for management of bone loss in prostate cancer patients. According to a recent statement by Brown *et al.* oral alendronate (70 mg/weekly) or oral riseondronate (35 mg/weekly) should be chosen as first-line intervention in the event of bone loss occurring upon introduction of ADT (*Brown et al.*, 2020). While these pharmacological agents should prove effective in majority of patients, in cases when oral therapy is not possible or poorly tolerated, intravenous zoledronic acid (5 mg/yearly) or subcutaneous denosumab (60 mg/six monthly) can be used instead (*Michaelson et al.*, 2007; *Smith et al.*, 2009). Furthermore, each treatment regimen should be accompanied with regular assessments of the extent and rate of bone loss in a patient undergoing ADT, which ought to be performed every 12–18 months (*Brown et al.*, 2020). Such insight can be gained with the use of FRAX® Fracture Risk Assessment Tool, which – despite being developed from a non-ADT-exclusive patient cohort – can provide a valid clinical method of monitoring a patient's bone homeostasis (*Hoff et al.*, 2017). In addition to clinical interventions, each ADT-treated prostate cancer patient should also be informed about lifestyle modifications, such as regular physical activity, adequate calcium intake (700–1200 mg/daily), and vitamin D supplementation

Table 1. Summary of percentage changes in bone mass density observed at different skeletal locations. Values of the most effective drugs at each site has been highlighted (*Joseph et al.*, 2019)

Therapeutic agent	Drug class	Change in bone mass after trials at different skeletal locations (%)		
		Lumbar spine	Hip	Femoral neck
Zoledronic acid	Bisphosphonates	8.1%	4.5%	4.7%
Alendronate		4.3%	0.9%	6.2%
Risendronate		12.7%	ND	0%
Raloxifene	SERMs	2.0%	3.7%	2.0%
Toremifene		2.3%	1.9%	1.9%
Denosumab	Monoclonal Antibody	7.1%	3.2%	3.9%

ND – no data, information not provided by the study; SERMs – selective oestrogen receptor modulators

(800 IU/daily) – all of which have been shown to decrease the risk of fractures to a statistically significant extent (*Bienz* and *Saad*, 2015).

Conclusions

The bone remodelling cycle is a complex biochemical mechanism that plays a central role in the maintenance of bone homeostasis. It provides the human skeleton with a remarkable ability to alter its phenotype throughout life, which protects its integrity in the face of changing mechanical requirements. Although not immediately evident, the process of bone remodelling is under continuous control of systemic hormones, such as androgens and oestrogen. The importance of this regulation can be best appreciated when looking at the markedly increased rates of skeletal disorders seen among prostate cancer patients undergoing androgen deprivation therapy. Whilst there currently seems to be a lack of scientific consensus on the precise aetiology of these pathological changes, further explorations into the intricate properties of the human bone might yield exciting discoveries that could contribute to the development of new clinical solutions in the future.

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