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VIEWPOINT

Prediction of fragility fractures in men with prostate cancer under androgen deprivation therapy: the importance of a multidisciplinary approach using a mini-invasive diagnostic tool

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Abstract

Bone fragility in men who are treated with androgen deprivation therapy (ADT) has a complex pathophysiology that differs from that of primary and post-menopausal osteoporosis. Fracture risk assessment based on bone mineral density (BMD) and Fracture Risk Assessment Tool (FRAX) score might not be effective in this patient setting, since high frequency of fragility fractures has been reported even in subjects with low FRAX risk and normal BMD. In this paper we want to emphasize the importance in the individual assessment of bone fragility and prediction of fractures by measuring parameters of bone quality, assessing morphometric vertebral fractures and evaluating body composition that in subjects under hormone-deprivation therapies can play a crucial role. Noteworthy, a single mini-invasive diagnostic tool, i.e., the dual energy x-ray absorptiometry (DXA) scan, offers the opportunity to evaluate reliably parameters of bone quality (e.g., trabecular bone score) and body composition, besides measurement of BMD and assessment of vertebral fractures by a morphometric approach. This article highlights the values and cost-effectiveness of this mini-invasive tool in the context of multidisciplinary approach to subjects with prostate cancer under ADTs.

Keywords Fractures · Androgen-deprivation therapy · Prostate cancer · FRAX · Body composition

Background

Skeletal fragility is an important clinical issue in men with non-metastatic prostate cancer undergoing treatment with androgen-deprivation therapies (ADTs). Fragility fractures develop in a remarkable number of subjects as consequence of exposure to ADTs and management of fractures in this clinical setting might be a challenge. Differently from the general population, dual-energy X-ray absorptiometry (DXA) measurement of bone mineral density (BMD) is generally unreliable in identifying individuals under ADTs at high risk of fractures [1]. In this setting, bone quality is impaired more than quantity and fractures frequently develop outside the context of a densitometric diagnosis of osteoporosis [2]. Use of techniques unable to detect alterations in bone microstructure, such as DXA measurement of trabecular bone score (TBS), might improve the management of skeletal fragility in subjects under hormone deprivation therapies [3], such as demonstrated for other forms of secondary osteoporosis [4]. In addition, recent studies have demonstrated that body composition has a major role in predicting bone fragility in a condition where sex hormones are depleted. Fat mass and lean mass should be taken into account in attribution of the fracture risk for men undergoing ADT [5].

Evaluation of fracture risk under ADTs

Indeed, although TBS has not been so far tested in the specific setting of ADTs, experience in subjects with hypogonadism suggests that fracture prediction might be

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improved by measuring this DXA parameter when skeletal fragility is related to testosterone deficiency [6]. Noteworthy, DXA can also be used for detection of fragility vertebral fractures (VFs) that are the hallmark of osteoporosis and are frequently underdiagnosed by a simple clinical approach [7]. Indeed, VFs occur frequently in men with prostate cancer before and during ADTs [2, 8]. It is well established that a prior VF is a strong risk indicator for subsequent vertebral and also nonvertebral fractures [9], an effect that could be amplified in individuals exposed to ADTs [10]. Therefore, including morphometric assessment of VFs together with TBS in the diagnostic work-up of subjects with prostate cancer could further improve prediction of fragility fractures [11].

Fracture Risk Assessment (FRAX) algorithm was developed to predict an individual's 10-year probability of major osteoporotic fracture and hip fracture from readily assessed clinical risk factors and optional BMD [12]. Use of FRAX in clinical practice informs the definition of fracture probability at which to recommend treatment – termed the intervention threshold. Guidelines have recommended that a fixed probability threshold of 20% for a major osteoporotic fracture be used as an intervention threshold [13]. Although initially developed for use in the general population, there is increasing interest in the application of FRAX to subjects with secondary osteoporosis. A recent study showed in individuals with prostate cancer a good agreement between the predicted and observed 10-year major osteoporotic fracture probability [14]. Indeed, the role of FRAX in subjects exposed to ADTs is uncertain. In the general population FRAX robustly predicts fractures and is not affected by variations in body composition [15]. It might not be the case in men exposed to ATDs [1].

Impact of body composition on fracture risk under ADTs

In the general population, low body mass index (BMI) is a well-recognized risk factor for fractures while higher BMI might have a beneficial effect [16]. However, the relationship between obesity and bone fragility is complex and is the result of the balance between two opposite effects: the protective one due to increased estrogen synthesis from androgens mediated by aromatase enzyme in fat tissue with consequent increase in BMD; and the detrimental one, due to the production of inflammatory cytokines altering bone remodeling and bone quality [5]. These two contrasting effects form the basis of the so-called paradox of obesity. In this context, the possible role of hypovitaminosis D and secondary hyperparathyroidism, that frequently occur in subjects with sarcopenic obesity and hypogonadism, might be considered in pathogenesis of skeletal fragility related to ADTs [17, 18]. In the general male population the effect of estrogens generally prevails and therefore obese subjects have a lower fracture risk than those with low BMI; however, when an overweight/obese man receives ADTs, the consequent reduction in BMD due to androgen and estrogen deprivation synergizes with the negative effect of adiposity on bone quality [5]. As a matter of fact, in men under ADTs high BMI was associated with higher prevalence of morphometric VFs [2]. In this scenario, the potential deleterious impact of decrease in lean body mass should be also considered [5].

In a small prospective study conducted by our group in patients with prostate cancer treated with the LHRH analog antagonist degarelix [19], a strong inverse correlation was found between appendicular lean mass index (ALMI), which is an expression of the muscle mass of the limbs, and C-terminal telopeptide of type I collagen (CTX), a marker of bone resorption, either at baseline or after treatment. More importantly, a significant inverse correlation between changes in ALMI and CTX and a direct relationship between changes of ALMI and ALP before and after degarelix were observed. These data support the existence of a functional and biological relationship between muscle and bone tissues and suggest that decrease in lean mass during ADT may influence bone remodeling, leading to bone quality deterioration.

Our belief is that, unlike primary osteoporosis, body composition, that is high fat body mass and low lean body mass, could play a major role in predicting the fracture risk in patients with prostate cancer undergoing ADT.

Conclusion

A holistic evaluation of skeletal health should be implemented in subjects with prostate cancer exposed to ADTs, including evaluation of body composition, TBS, VFs along with measurement of BMD and evaluation of concomitant risk factors of skeletal fragility. Interestingly, DXA is a tool that allows to monitor body composition and bone health through low exposure of patients to X-rays and a low economic cost.

Through periodic monitoring with DXA of patients with prostate cancer during hormone deprivation therapies, it is possible to calibrate preventive measures (diet and physical activity) at an individual level and this may result in an improvement in quality of life as well as effective prevention of complications both cardiovascular and skeletal. It is therefore necessary that the bone specialist follows the patient with prostate cancer and join the multidisciplinary team responsible for the management of this patient.

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Compliance with ethical standards

Conflict of interest The authors declare no competing interests.

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