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EDITORIAL

Minimizing the risk of sarcopenic obesity during androgen deprivation therapy—promising results for men treated with GnRH antagonists

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It is estimated that about 50% of men with advanced and metastatic prostate cancer will receive standard of care androgen deprivation therapy (ADT) during the course of their disease [1]. While ADT delays prostate cancer progression, alleviates cancer-related symptoms and prolongs life in some men with prostate cancer, it is also associated with known side effects that increase the risk of frailty and co-morbidities (e.g. diabetes and cardiovascular disease (CVD)). Administration of gonadotropin-releasing hormone (GnRH) agonists and antagonists are medical means to downregulate testosterone production with a common goal of achieving castrate levels of testosterone [2]. While both modes of ADT are effective in disrupting the hypothalamic–pituitary–gonadal axis to induce hypogonadism, they do so through different mechanisms that vary in their impact on follicle-stimulating hormone (FSH) and testosterone levels. Specifically, GnRH antagonists produce an immediate, sustained suppression of FSH (>90% reduction) and testosterone. In contrast, GnRH agonists generally take several weeks to induce castrate levels of testosterone and only after provoking an initial transient surge in FSH and testosterone (known as flare) [3]. These differential effects are increasingly viewed as potential factors in determining the differences in the adverse effects reported with the two modalities of ADT. Changes in body composition and metabolic dysfunction, including insulin resistance and dyslipidemia, have been extensively studied during GnRH agonist administration and are known to increase risks of frailty, diabetes and CVD. GnRH antagonists, on the other hand, have been less well studied, though more favourable outcomes have been reported for cardiovascular risk and diabetes [4]. GnRH antagonist impact on body composition has not been studied.

In this issue of *Prostate Cancer and Prostatic Diseases*, Palumbo et al. [5] report results from the Bone mineraL, mAss, Dexa, dEgarelix (BLADE) single-centre, single-arm phase IV clinical study that provide interesting new insights into the systemic changes associated with the GnRH antagonist degarelix which suggests potential advantages over GnRH agonists. Men with non-metastatic prostate cancer ($N = 29$; median age 71, interquartile range 63–79 years), eligible for ADT, were treated with monthly subcutaneous injections of degarelix for 12 months. They underwent baseline and 12-month dual-energy x-ray absorptiometry (DEXA) scans for assessment of fat body mass (FBM) and lean body mass (LBM) and for analyses of appendicular lean mass index (ALMI) and the ALMI/FBM ratio, a proxy for sarcopenic obesity [6]. In addition, serum lipids, glycemic control and FSH were measured at baseline, 6 months and 12 months. The main findings showed a mean difference in FBM from baseline to 12 months, corresponding to an increase of 13.8% ($p < 0.001$), with LBM and ALMI remaining stable, and the ALMI/FBM ratio decreasing by 24.7% ($p < 0.001$). Mean total cholesterol, high-density lipoprotein (HDL) and triglyceride levels were unchanged during the 12-month follow-up and although glucose levels remained stable, glycated haemoglobin increased by 6.9% ($p < 0.001$) at 6 months and 8.9% ($p < 0.001$) at 12 months relative to baseline. Steep declines were observed for FSH with mean differences of −87.9% ($p < 0.001$) and −79.8% ($p < 0.001$), at 6 months and at 12 months, respectively. Furthermore, while a correlation was not found between ALMI and FSH at baseline or at 12 months, there was a statistically significant inverse correlation between ALMI/FBM and FSH at 12 months ($r = -0.44$, $p = 0.017$); in other words, lower levels of FHS were correlated with higher ALMI/FBM ratios.

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Sarcopenia is an age-related condition characterised by a gradual atrophy of skeletal muscle mass accompanied by a reduction in muscle strength and function. While sarcopenia itself increases the risk of falls, CVD and mortality, risks are further increased in the presence of sarcopenic obesity which is additionally characterised by the presence of excess adiposity [7]. Men with prostate cancer receiving ADT are a particularly vulnerable group at risk of developing sarcopenic obesity, given that age-related body composition changes may be exacerbated by medically induced hypogonadism. Indeed, Smith et al. [8] reported that men ≥70 years of age lost greater amounts of muscle mass during a 3-year study of ADT compared with men <70 years.

The study by Palumbo et al. [5] showing maintenance of LBM following 12 months of treatment with degarelix (in men with a median age of 71 years) is in contrast to most studies of GnRH agonists. A systematic review of studies reporting DEXA-derived body composition changes during ADT reported consistent decreases in LBM (mean loss of 2.8%, $p < 0.0001$) and increases in FBM (7.7%, $p < 0.0001$), though substantial heterogeneity in study designs were noted [9]. Furthermore, in a study similar to BLADE, in men with non-metastatic prostate cancer initiating ADT (type of ADT was not specified but assumed to comprise mostly of GnRH agonists given current practice), DEXA-derived LBM loss was estimated to be 3% ($p = 0.03$) at 12 months and FBM gains were about 14% ($p < 0.001$) at 12 months relative to baseline [10]. Though the study by Palumbo et al. [5] was not designed to investigate the mechanistic underpinnings of the effects of degarelix on body composition, the inverse correlation between FSH and ALMI/FBM is an intriguing finding that suggests a possible link that warrants further study.

In addition to the preservation of LBM, it is worth noting that there may also be a more favourable metabolic health profile with degarelix administration compared with GnRH agonists owing to stable levels of total cholesterol, HDL and triglyceride levels observed throughout the 12 months. While HDL levels did not increase, as often observed with GnRH agonists and may be viewed as a disadvantage, the cardioprotective effect of HDL in the presence of low testosterone levels has been questioned [11]. BLADE, however, is a small study and the individual metabolic response patterns suggest a variability in responses that is important to investigate further in men treated with GnRH antagonists (Supplementary Fig. 2, Palumbo et al. [5]).

To conclude, the results from the study by Palumbo et al. [5] suggest that for some men for whom ADT is indicated, GnRH antagonists may be associated with fewer adverse effects than treatment with GnRH agonists. Importantly, the results for body composition, specifically the overall maintenance of LBM, bode well for minimizing sarcopenic obesity and potentially more favourable long-term outcomes with GnRH antagonists than with GnRH agonists in the management of prostate cancer.

Compliance with ethical standards

Conflict of interest The author declares no competing interests.

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