Review article

The potential role of follicle-stimulating hormone in the cardiovascular, metabolic, skeletal, and cognitive effects associated with androgen deprivation therapy

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Abstract

\textbf{Purpose:} To explore how follicle-stimulating hormone (FSH) may contribute to cardiovascular, metabolic, skeletal, and cognitive events in men treated for prostate cancer, with various forms of androgen deprivation therapy (ADT).

\textbf{Materials and methods:} A colloquium of prostate cancer experts was convened in May 2015, to discuss the role of FSH in the development of unwanted effects associated with ADT. Subsequently, a literature review (Medline, PubMed, and relevant congress abstract databases) was performed to further explore and evaluate the collected evidence.

\textbf{Results:} It has become evident that, in the setting of ADT, FSH can promote the development of atherosclerotic plaque formation, metabolic syndrome, and insulin resistance. Data also suggest that FSH is an important mediator of bone remodeling, particularly bone resorption, and thereby increases the risk for bone fracture. Additional evidence implicates a role for FSH in bone metastasis as well. The influence of FSH on ADT-induced cognitive deficits awaits further elucidation; however, the possibility that FSH may be involved therein cannot be ruled out.

\textbf{Conclusions:} The widespread molecular and physiological consequences of FSH system activation in normal and pathological conditions are becoming better understood. Progress in this area has been achieved by the development of additional investigative and clinical measures to better evaluate specific adverse effects. More research is needed on FSH function in the development of cancer as well as its association with cardiovascular, metabolic, musculoskeletal, and cognitive effects in ADT. © 2017 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

\textbf{Keywords:} Follicle-stimulating hormone (FSH); Prostate cancer; Cardiovascular; Bone; Metabolic syndrome; Cognition

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1. Introduction

Recent advances, which have elucidated the role of follicle-stimulating hormone (FSH) in various malignancies, have also expanded our understanding of the effect of FSH-related effects produced by gonadotropin-releasing hormone/luteinizing hormone (LH)-releasing hormone (GnRH/LHRH) receptor agonists and antagonists used in the treatment of prostate cancer. Normally, GnRH/LHRH is released in a pulsatile manner from the hypothalamus, binds to the GnRH/LHRH receptor in the anterior pituitary, and induces the release of LH and FSH. The prostate, as well as other tissues, can also synthesize and release FSH, and express FSH receptors (FSHR) [1–3]. There is evidence that benign prostatic hyperplasia (BPH), as well as advanced and metastatic prostate cancer tissue, has either greater FSH or FSHR expression or both than healthy tissue. Using immunohistochemical techniques in primates and rodents, Garde et al. [4] demonstrated that FSHR antibody staining was greater in BPH and malignant prostate cancer tissue, compared with healthy tissue. In a similar experiment, Ben-Josef et al. [5] reported FSHR expression increased as a function of disease severity (normal prostate tissue < BPH < primary carcinoma), and prostate cancer cell lines that do not express the androgen receptor (AR), but not normal prostatic tissue, also stained positive for FSHR. Consistent with these findings, clinical studies demonstrated positive correlations among serum FSH concentration, tumor malignancy status, and tumor size [6]. Moreover, following tumor development, serum FSH was a significant predictor of extraprostatic extension [7] and the time to the development of castrate-resistant prostate cancer [8].

Functional FSHR expression has been identified in the androgen insensitive prostate cancer cell lines, PC3, and DU145 [5]. Both prostatic- and pituitary-derived FSH act directly on prostatic FSHR, which may then modulate hormones and growth factors involved in the development of BPH [5]. Interestingly, FSHR expression, together with vascular endothelial growth factor (VEGF) expression, has been identified on endothelial cells of a wide array of tumors (e.g., breast, urinary bladder, colon, pancreas, and testes) [9], and likely contributes to metastatic processes including intravasation and angiogenesis [10,11]. FSH is a potent inducer of reactive oxygen species [12], which are also involved in the expression and regulation of VEGF and angiogenesis [13]. VEGF has a critical role in enhancing neovascularization of growing tumors and was found to be overexpressed in BPH and highly overexpressed in prostate cancer (for reviews on VEGF and prostate cancer see Refs. [14–17]). In summary, FSH acts as a mitogen [18] and a positive trophic factor in tumor angiogenesis [19–21]. This combined effect is important to consider because detailed studies have linked stimulation of FSHR with downstream activation of VEGF [22], and the transmigration of malignant prostate cancer cells into circulation [23].

Although androgen deprivation therapy (ADT) improves outcomes in men diagnosed with advanced prostate cancer, and those treated with radiation for high-risk localized disease, it is also associated with adverse treatment-related metabolic effects, increased cardiovascular morbidity and mortality [24,25], and decreased bone mineral density [26,27]. Accumulating experimental and clinical data indicate that FSH may contribute to development of these unwanted effects through its role in inflammation, atherosclerosis, insulin resistance, formation of reactive oxygen species, and adipocyte rearrangement [12,28–30]. The purpose of this review is to investigate the potential associations between FSH and the cardiovascular, metabolic, skeletal, and cognitive effects associated with ADT for prostate cancer (Table).

2. Methods

A colloquium of world experts in FSH, GnRH/LHRH, endocrinology, cardiovascular function, and prostate cancer was convened in May 2015 to discuss current knowledge of FSH, the relevant evidence for its role in the progression of prostate cancer, and the unwanted effects associated with ADT. We also conducted a comprehensive literature search of Medline, PubMed, and relevant congress abstract databases using combinations of the keywords such as prostate cancer, follicle-stimulating hormone, metabolic syndrome, cognition, cardiovascular disease (CVD), vascular endothelial growth factor, neoangiogenesis, bone metabolism, metastases, androgen deprivation therapy, and gonadotropin releasing hormone/luteinizing hormone-releasing hormone agonists/antagonists. Basic science and clinical studies that reported an association between the FSH system, and adverse consequences of prostate cancer, and its treatment with ADT were selected for further review. Data from relevant and FSH-focused studies were presented, reviewed, and discussed in detail by the authors. In addition, an updated review of the literature was conducted periodically during the writing of this article.

Table
Representative articles summarizing the unwanted effects associated with androgen deprivation therapy and their relationship to follicle-stimulating hormone.

<table>
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<th>Effect of ADT</th>
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<td>Cardiovascular morbidity and mortality</td>
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<td>Metabolic syndrome</td>
<td>Adipocyte rearrangement, metabolic derangement, and insulin resistance</td>
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<td>Bone loss, fracture, and metastasis</td>
<td>Increased osteoclast expression through RANK- and TNF-α-mediated pathways</td>
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<td>Cognitive impairment</td>
<td>Associated with decreased testosterone and increased FSH and LH levels</td>
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3. Basis of chemical ADT in the treatment of prostate cancer

The GnRH/LHRH receptor is the target of agonists and antagonists in the treatment of androgen-dependent prostate cancer. During the past 43 years, more than 3,000 agonistic analogs of GnRH/LHRH have been synthesized, and much has been learned about the structure-activity relationship of these molecules, thus enabling the synthesis of ligands with greater potency, selectivity, and resistance to enzymatic degradation [31–33]. Several of these analogs have progressed into clinical application and have been successfully used for ADT in the treatment of prostate cancer. At the same time, hundreds of GnRH/LHRH receptor antagonists were also synthesized and evaluated in preclinical and clinical studies [31,34,35]. Following early setbacks with the use of molecules that produced anaphylactic reactions, several improved GnRH/LHRH receptor antagonists were synthesized that demonstrated clinical efficacy, without those side effects, in patients with prostate cancer and BPH [31,34,36–39]. Preclinical studies demonstrated that GnRH/LHRH receptor antagonists inhibited tumor growth, lowered levels of testosterone, and decreased prostate-specific antigen to a greater extent than did GnRH/LHRH receptor agonists [31,32,40,41].

Preliminary clinical trials with GnRH/LHRH receptor antagonists confirmed their positive therapeutic profile [42], and subsequent side-by-side comparisons with GnRH/LHRH receptor agonists showed a modest advantage for antagonist therapy. GnRH/LHRH receptor antagonists lowered testosterone to castrate levels more rapidly, without “flare” reactions, and dramatically decreased both LH and FSH [38,43–45]. GnRH/LHRH antagonists also suppressed serum levels of FSH and LH more rapidly than did agonists. However, although there were no appreciable differences between treatments in LH concentrations measured over 1-year treatment period, serum FSH concentration increased in the agonist arm relative to the antagonist by day 28; this difference continued through day 364 [45]. Importantly, the relative difference in magnitude and duration of FSH suppression with GnRH/LHRH antagonists is not ligand specific (i.e., exclusive to a specific molecule), but rather is a class effect associated with the mechanism of action of all clinically evaluated antagonists [46]. These GnRH/LHRH analogs have served as both therapeutics and as tools for investigating the underlying mechanisms responsible for treatment differences.

4. Association between FSH and cardiometabolic morbidity

For several years accumulating clinical data have indicated that ADT has been associated with potentially serious unwanted effects, including an increased risk for cardiovascular morbidity and mortality [24,25,47,48]. Most reports are based on observational data, but potentially owing to differences in treatment interventions and disease heterogeneity, post hoc analyses performed on randomized trials have not unequivocally supported such an association between ADT and cardiac death [49,50]. Particularly, patients with pre-existing CVD seemed to be at risk for the development of cardiovascular events with ADT. Accordingly, data from O’Farrell et al. [51] found that men undergoing ADT, who have pre-existing risk factors for CVD are at greater risk for adverse cardiovascular outcomes compared with those without pre-existing risk factors. It has been suggested that the risk for CVD and cardiac events may be stratified based on the patient’s cardiac history, and that symptoms can develop soon after initiating ADT [51].

In patients without established cardiovascular risk factors, ADT can promote the development of proatherogenic metabolic derangements, such as glucose intolerance, dyslipidemia, and increased adiposity [52], in an exposure-dependent manner [53,54]. This increased cardiovascular risk associated with chemical ADT was once thought to be a consequence of hypogonadism [54,55]. More recently, however, reports highlighting the potential differences in cardiovascular risk between GnRH/LHRH agonists and antagonists [56] have led some investigators to focus on ligand-specific mechanisms such as T lymphocyte (Fig. 1A) or cardiac GnRH/LHRH receptor activation, as well as the role of the FSH system in mediating cardiovascular effects (reviewed by Zareba et al. [57]).

There are a number of processes involved with ADT-associated cardiometabolic morbidity that FSH may influence, including metabolic alterations favoring adiposity. For example, Liu et al. [29] studied age-dependent changes in circulating FSH levels and their correlation with body mass index. They reported the presence of FSHR in human adipose tissue and on adipocytes, along with a positive correlation between FSH levels and an increase in body mass index. Further support for the role of FSH in cardiometabolic morbidity can be found in preclinical and in vitro experiments. Murine 3T3-L1 preadipocytes treated with recombinant FSH in vitro manifested an up-regulation in the expression of lipogenic genes, including fatty acid synthase and lipoprotein lipase, the major mediators of lipoprotein-dependent fatty acid uptake in adipose tissue [58]. Additionally, studies in mice showed that dysfunctional fat in vivo accumulates in a FSHR concentration-dependent manner [29]. Adipose tissue itself may have a role in cardiovascular dysfunction. Adipokines, such as tumor necrosis factor alpha (TNF-α) and interleukin-6 (IL-6), are proinflammatory molecules secreted by adipocytes that are associated with the development of insulin resistance and atherosclerotic disease [28].

Data from in vivo preclinical research support the potential ligand-dependent effect of ADT on cardiometabolic morbidity. Low-density lipoprotein receptor knockout (LDLR−/−) mice treated with different modes of ADT
(orchietomy, GnRH/LHRH antagonist, or agonist) for 4 months, showed no appreciable differences in testosterone suppression [59]; however, mice treated with antagonist had significantly lower levels of FSH compared with animals treated with agonist or surgical castration. Mice treated with GnRH/LHRH antagonist accumulated the lowest percentage of adipose tissue compared with mice treated with agonist or orchietomy; those treated with GnRH/LHRH agonist or orchietomy had more than double the number of atherosclerotic plaques compared with those of the antagonist arm. The fasting serum lipid profiles of these mice showed treatment with the GnRH/LHRH receptor antagonist resulted in the highest levels of high-density lipoprotein and the lowest low-density lipoprotein concentrations compared with the other treatment groups [59]. Lastly, all mice developed fatty streaks in the ascending aorta, but the necrotic areas within the atherosclerotic plaques were significantly smaller in mice treated with GnRH/LHRH antagonist, compared with those treated with agonist or orchietomy. This study demonstrates that the cardiometabolic differences among modes of ADT can be recapitulated in murine models, and the results suggest that important changes in cardiometabolic markers in the context of ADT may not be explained by the effects of low testosterone alone.

Knutsson et al. [60] reported similar effects on lipids in apolipoprotein knockout (ApoE\(^{-/-}\)) mice, where the GnRH/LHRH receptor agonist significantly increased the size of areas of necrosis and the degree of inflammation in atherosclerotic plaques compared with controls. Consistent with these findings, Moulton et al. [61] reported that an angiogenesis inhibitor reduced plaque growth and intimal neovascularization in ApoE\(^{-/-}\) mice, suggesting neovascularization itself is associated with plaque development. This is noteworthy because FSHRs are located on neovascular endothelium [9] and FSH promotes angiogenesis through a VEGF-dependent mechanism [56,62]. Lastly, vascular calcification, which is also associated with atherosclerosis and subsequent plaque disruption, may be partially driven by FSH signaling. Data have also shown that calcified atherosclerotic plaques are at least 4- to 5-times more stiff than cellular plaques [63], and physical stress directed at the interface between calcified and vulnerable, adjacent, noncalcified regions, are more likely to result in plaque instability and subsequent rupture [64]. Osteoclasts, through a signaling cascade involving FSH (detailed in the following section), can reabsorb calcified regions within plaques further increasing the likelihood of rupture (Fig. 1B and C).

In summary, the proinflammatory effects of FSH, as well as FSH-mediated alterations in adipocyte composition and adipokine release, provide a potential mechanism for ADT-induced cardiometabolic changes observed in prostate cancer treatment. Experimental research in mice, supported by emerging clinical data, demonstrates GnRH/LHRH agonists and antagonists not only differ in their mechanism of action at the receptor level but also in their effects downstream (e.g., FSH). These differences may be important when treating patients with pre-existing risk factors for CVD [56]. Additional clinical research is needed to confirm these hypothesized differences between pharmacologic
modes of ADT and the specific effect of FSH on cardiometabolic morbidity.

5. Association among FSH, bone metabolism, and bone metastasis

The association between ADT and bone loss has been recognized for many years [26,65]. Increased bone loss and fracture incidence are partially the result of lower levels of testosterone available for conversion to estrogen, which is inversely related to osteoclast activity [65,66]. Although the posited influence of FSH on cardiometabolic morbidity is novel, and perhaps surprising, an association between FSH and bone metabolism was previously identified in women with postmenopausal osteoporosis. Clinical studies in postmenopausal women revealed an inverse relationship between serum FSH and bone mineral density as well as markers of bone resorption [30,67]. Likewise, in a cross-sectional, case-control study of 156 men, a significant negative correlation was identified between FSH and bone mineral densities in the lumbar spine and femoral neck [68].

Under normal physiologic conditions, bone metabolism involves a complex sequence of bone turnover (via osteoclasts) and bone formation (via osteoblasts). Osteoclasts resorb the mineral components of bone via an acidic extracellular mechanism, resulting in the release of a number of factors from the bone matrix, including transforming growth factor beta (TGFβ) [69]. Osteoblasts are stimulated by these osteoclastic soluble factors, and then deposit osteoids (organic, young bone matrix that has not undergone calcification) at the resorption site [70]. Research has identified a number of cytokines and signaling molecules, such as receptor activator of nuclear factor kappaB (RANK), RANK ligand (RANKL), osteoprotegerin, TNF-α, and IL-6, that are critical in this process; however, several of these proteins are either directly or indirectly affected by FSH (Fig. 2A) [30,71–73].

Preclinical and in vitro studies also support a role for FSH in bone metabolism. FSHR activation directly stimulates the expression of RANK on the surface of monocyte osteoclast precursors, which can be transformed into osteoclasts following activation by RANKL [72]. The expression of RANKL may be increased through FSH signaling or GnRH/LHRH receptor agonist stimulation of T cells (Fig. 2B) [71,74]. FSH has also been shown to induce release of TNF-α from mononuclear cells, bone marrow granulocytes, and macrophages, which can independently stimulate osteoclast precursors to differentiate into osteoclasts (Fig. 2C) [71]. FSH has also been shown to stimulate release of IL-1β from monocytes [30], which increases survival time of mature osteoclasts, thereby allowing them to participate in additional rounds of resorption [75]. These data provide hypothesized mechanisms by which FSH may mediate bone loss and increase fracture risk in patients with prostate cancer.

Increased FSH-mediated osteoclast activity also has the potential to enhance the growth and progression of bone metastases [72]. Once metastatic prostate cancer cells arrive in bone, they are stimulated by growth factors, such as TGFβ, present in the noncellular fraction of bone marrow [76]. RANKL, also present in the bone microenvironment, stimulates metastatic prostate cancer cells to release IL-6 [73], which signals continued release of IL-6 through a feed-forward mechanism, as well as matrix metalloproteinase-9 (MMP9) [77], a protease known to facilitate tumor cell migration and invasion. Factors released from the bone matrix in response to osteoclastic degradation (e.g., calcium, endothelial growth factor, basic fibroblast growth factor, and TGFβ) then stimulate osteoblastic differentiation and activity (Fig. 2D). Clinically, prostate cancer skeletal metastases are usually characterized radiographically as osteoblastic and result in new bone that is of poor quality, immature, and of a woven configuration [78]. The combination of dysregulated osteoblastic and osteoclastic function coupled with metastatic invasion of bone, is consistent with the hypothesized alterations in bone metabolism mediated through FSH signaling [78].

In patients with metastatic prostate cancer, elevated levels of serum bone–specific alkaline phosphatase, a marker of osteoblastic activity, are significantly associated with shorter overall survival [79]. Clinical and experimental evidence indicates bone resorption, which is also paradoxically increased in osteoblastic metastases. Concentrations of the bone resorption marker, N-telopeptide, likewise is known to be elevated in patients with prostate cancer and is also a strong predictor of morbidity and mortality [80]. Distinct ADT modalities may have different effects on the clinical course of bone metastases. In a retrospective analysis of a prospective, randomized, pivotal trial comparing GnRH/LHRH receptor agonists and antagonist in 610 patients with advanced prostate cancer, among patients with metastases or baseline prostate-specific antigen levels > 50 ng/ml or both, serum alkaline phosphatase levels were significantly reduced in patients treated with the GnRH/LHRH receptor antagonist vs. agonist [81,82]. At the completion of the study (day 364), there remained a significant difference in levels of serum alkaline phosphatase between the 2 kinds of ADT. Although these findings need to be confirmed with larger-scale, well-controlled, clinical trials, these data suggest that FSH suppression in the context of ADT should be further evaluated in conjunction with a strategy for optimizing bone health.

6. Association between ADT and cognitive impairment

Clinical research on the effect of ADT continues to expand as the average male life expectancy increases. A systematic review of the literature investigating effects of ADT on cognition indicates that upwards of 69% of patients exhibit a measurable decline in at least 1 cognitive domain.
with the most common impairments found in visual-spatial and executive function [83]. In a controlled comparison of 58 men undergoing ADT, the likelihood of exhibiting cognitive dysfunction within 6 months of initiating treatment was 70% higher than age-matched controls who either had undergone prostatectomy or did not have prostate cancer [84]. Evidence that testosterone generally has procognitive effects are consistent with these findings. Men exhibiting symptoms of dementia were found to have lower serum testosterone when compared with age-matched controls [85]; however, reduced testosterone was also identified as a risk factor for the development of Alzheimer’s disease [86,87]. In animal models, testosterone demonstrated neuroprotective effects in brain nuclei important for cognition; moreover, testosterone through an AR activation was shown to ameliorate damage caused through oxidative stress [88], and to limit neuronal apoptosis in the hippocampus [89,90]. This neuronal effect is believed to occur through AR-mediated stimulation of mitogen-activated protein kinase, and subsequent phosphorylation of Bcl2-associated-protein-of-cell-death, a proapoptotic protein, by ribosomal S6 kinase [91,92]. Finally, testosterone has been shown to disrupt the formation of beta-amyloid accumulation through several mechanisms, including testosterone-induced up-regulation of membrane metalloendopeptidases [93,94], (which break down beta-amyloid), and a down-regulation of beta-secretases (which support beta-amyloid accumulation) [95].

The role of gonadotropins in the pathogenesis of cognitive dysfunction and disease remains relatively unexplored, despite the well-defined relationship between androgens and gonadotropins. In a small study, serum levels of FSH and LH in 40 male residents of long-term care facilities with a primary diagnosis of dementia were significantly higher compared with 29 age-matched controls [85]. Consistent with these results, elevated concentrations of FSH and LH have also been reported in patients with Alzheimer’s disease [96,97]. Interestingly, animal studies suggest that the effect of ADT on cognition may be treatment dependent. Although GnRH/LHRH receptor agonists are thought to increase depression and worsen memory, there is some evidence that antagonists are
protective of brain function [98]. In a murine model, the GnRH/LHRH receptor antagonist, cetrorelix, reversed beta-amyloid-induced memory impairment and was also found to exhibit anxiolytic and antidepressive effects [99].

The effect of ADT on cognitive performance, especially in the elderly, is intriguing, although the mechanisms accounting for these differences are currently unknown. Nonetheless, as we holistically evaluate individualized treatment options in the context of ADT, it is reasonable to hypothesize that FSH might play a role. Further studies comparing cognitive functions in patients with prostate cancer treated with GnRH/LHRH receptor agonists and antagonists are warranted to learn whether cognitive impairment varies as a function of ADT modality.

7. Summary and conclusions

The availability of different pharmacologic strategies to attain ADT has progressively helped to identify various mechanisms, beyond testosterone suppression, to help optimize treatment and potentially reduce unwanted side effects. Men who undergo ADT for prostate cancer appear to be at higher risk for developing cardiovascular morbidity, metabolic syndrome, musculoskeletal events, and cognitive impairment. Converging lines of research have revealed a potential role for FSH in several of these processes. Evidence that GnRH/LHRH receptor antagonist effects can be differentiated from those of agonists in suppressing the FSH system in ADT might provide a selective mechanism of therapeutic action to consider in optimizing treatment for patients with prostate cancer.

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