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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

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).

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.

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.

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.

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 tumor cells 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.

Effect of ADT	Potential role of FSH	References
Cardiovascular morbidity and mortality	Dyslipidemia, plaque formation, and disruption	[25,49–51,57]
Metabolic syndrome	Adipocyte rearrangement, metabolic derangement, and insulin resistance	[28,29,48,52,54]
Bone loss, fracture, and metastasis	Increased osteoclast expression through RANK- and TNF-α-mediated pathways	[26,70,71,78,81]
Cognitive impairment	Associated with decreased testosterone and increased FSH and LH levels	[84,85,87,89,91]