The role of FSH and LH in prostate cancer and cardiometabolic comorbidities

E. David Crawford, MD,1 Andrew V. Schally, PhD2
1Division of Urology, University of California San Diego, La Jolla, California, USA
2Division of Medical Oncology and Division of Endocrinology, Sylvester Comprehensive Cancer Center, Miller School of Medicine, University of Miami, Florida, USA

Introduction

Working synergistically, follicle-stimulating hormone (FSH) and luteinizing hormone (LH) may be directly involved in the development and progression of prostate cancer, which is the second most common type of cancer afflicting men in the United States.1 Approximately 33,000 U.S. men will die of prostate cancer in 2020, the CA: A Cancer Journal for Clinicians has predicted.1

Several studies have implicated dysregulation of the FSH system as a whole in both the initial development and progression of prostate cancer, and the development of castration-resistant prostate cancer (CRPC).3-5 Meanwhile, a growing body of research suggests that the elevated cardiovascular and metabolic risk associated with long-term androgen deprivation therapy (ADT) may at least partly be explained by FSH levels. This article details the possible role of the gonadotropin-releasing hormone/luteinizing hormone-releasing hormone (GnRH/LHRH) system, including FSH, on prostate cancer and cardiovascular comorbidities, as well as the impact of GnRH agonists and antagonists in these areas.

Specifically, we hypothesize that the increased cardiovascular risk associated with ADT may be explained through ligand-specific mechanisms


Introduction: In this article we advance a potential explanation for the incidence of cardiovascular (CV) and cardiometabolic risk in patients undergoing androgen deprivation therapy (ADT) for prostate cancer. Our conceptual model involves the differential impact of gonadotropin-releasing hormone (GnRH) agonists and antagonists on the follicle-stimulating hormone (FSH) system.

Materials and methods: Authors searched online repositories and meeting abstract databases for relevant materials.

Results: Mounting evidence links FSH with development and progression of prostate cancer. What is also becoming clear is that the differential effects of GnRH agonists and antagonists on FSH may at least partially explain the differing effects these agents have on CV risk during ADT. While GnRH antagonists immediately suppress FSH, GnRH agonists provoke a transient surge in FSH that may contribute to the higher CV risk observed with these agents. Additionally, recent studies suggest that GnRH antagonists may significantly reduce CV risk compared to GnRH agonists, particularly in men with pre-existing CV disease.

Conclusions: Patients with cardiovascular risk factors who require ADT may benefit from the better control of FSH provided by GnRH antagonists. ADT itself appears to heighten CV risk, and data suggest that FSH may at least partly drive this risk by promoting inflammation, atherosclerosis, insulin resistance, adipocyte rearrangement and plaque instability.

Key Words: prostate cancer, follicle-stimulating hormone, gonadotropin releasing hormone, cardiovascular diseases

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Address correspondence to Dr. E. David Crawford, University of California San Diego, Koman Family Outpatient Pavilion, La Jolla, CA 92037 USA
resulting in destabilization of atherosclerotic plaques, and that GnRH antagonists may carry less such risk than do GnRH agonists due to differences in these drugs’ mechanisms of action.

In formulating this hypothesis, the authors searched PubMed and relevant meeting abstract databases through August 2019 using keywords and combinations including prostate cancer, follicle-stimulating hormone/FSH, gonadotropin-releasing hormone (GnRH)/luteinizing hormone-releasing hormone (LHRH), GnRH agonists, GnRH antagonists and cardiovascular events/comorbidities.

**FSH system dynamics**

To date, the increased cardiovascular risk associated with ADT has been considered a byproduct of ADT-induced hypogonadism. FSH and LH are heterodimeric glycoproteins of the same class as thyroid-stimulating hormone and human chorionic gonadotropin.6 LHRH is secreted from the preoptic area of the hypothalamus and reaches the pituitary via the portal system. In response, the pituitary secretes LH and FSH into the bloodstream. LH stimulates receptors on Leydig interstitial cells in the testes to induce testosterone production.7,8 Specifically, LH1 promotes the conversion of cholesterol to testosterone, which exerts negative feedback on the hypothalamus and pituitary gland.

FSH acts on the tubules to produce sperm and release inhibin, activin and follistatin. As their names suggest, inhibin and activin suppress and increase FSH secretion from the pituitary, respectively. Follistatin binds activin, thereby reducing FSH secretion. Other intrinsic FSH modulators include prostatic inhibin peptide (PIP) and regulators of G-protein signaling (RGS) proteins.6

Traditionally, FSH was believed to be synthesized and secreted only from the anterior pituitary, in response to the binding of GnRH/LHRH to its receptor. However, research published during the 1980s and 1990s identified extrapituitary sources of FSH including the prostate, testes, gastrointestinal tract and breast.9–11

**Possible role of FSH in prostate cancer**

Owing to Huggins and Hodgins’ seminal work, clinicians treating prostate cancer initially focused on manipulating androgens such as dihydrotestosterone, testosterone and estrogens. More recent research has identified key roles for non-androgenic hormones in prostate physiology and pathophysiology. For example, it has long been apparent that benign and malignant human prostate cells generate FSH and its receptor. Additionally, as prostate cells become less differentiated as men age, concentrations of both FSH and its receptors in prostate tissue increase.9,12 FSH induces dose-dependent increases in prostate-specific antigen (PSA) within prostatic tissue.13

A growing body of evidence links FSH and FSH receptor expression levels with prostate cancer aggression. For example, research shown FSH receptor expression to be low or undetectable in normal prostate tissue and benign prostatic hyperplasia (BPH), versus consistently high FSH receptor gene expression in prostate cancer samples, suggesting that receptor gene expression may increase with cancer progression. Dense expression of FSH receptors at the periphery of tumors suggests that these receptors may be relevant to the metastatic process.14 In other research, samples from 250 men with histologically confirmed prostate cancer revealed significantly higher serum FSH levels (7.07 ± 0.65 U/L versus 5.63 ± 0.31 U/L, p < 0.05) in those with locally advanced prostate cancer.15

Among metastatic tumors arising from six different primary tumors in the lung, breast, colon and other tissues, Siraj et al showed that 60%-70% of blood vessels associated with prostate cancer metastases in the brain and lymph nodes stained positive for FSH receptors. Investigators found no such FSH receptor expression in non-tumoral tissue of healthy patients.16

Additionally, the presence of FSH receptors on the luminal endothelial surface of prostate cancer cells noted by Radu et al suggests that FSH may play a role in tumor intravasation, the process by which malignant cells penetrate the endothelium and enter the circulation.17 The fact that exogenous FSH can stimulate proliferation of androgen-independent metastatic prostate cancer cell lines that lack androgen receptors10 also suggests that the FSH receptor and its ligand may influence the growth of CRPC.

Downstream, FSH acts as an important mitogen and a positive tropic signal for tumor angiogenesis through its influence on vascular endothelial growth factor (VEGF).18,19 Like FSHR expression, VEGF expression has been identified on endothelial cells of many types of tumors (breast, bladder, colon, pancreas and testes).14 VEGF plays a crucial role in neovascularization around growing tumor cells and is highly overexpressed in prostate cancer and, to a lesser extent, BPH.20 Studies have linked FSHR stimulation with downstream VEGF activation21 and the transmigration of malignant prostate cancer cells into the circulation.22

**Impact of ADT**

The initial discovery that hormones govern prostate size and function, and the observation that androgen production influences prostate cancer growth, provide...
the rationale for ADT. The National Comprehensive Cancer Network, American Urological Association and European Association of Urology all recommend ADT as primary systemic therapy for advanced and metastatic disease, and as adjuvant therapy in localized or locally advanced prostate cancer.

By medically manipulating GnRH/LHRH, ADT seeks to reduce serum testosterone to levels produced by bilateral orchiectomy. Consensus, backed by modern assays showing that bilateral orchiectomy actually produces testosterone levels around 15 ng/dL and by data demonstrating improved survival with lower testosterone levels, has dropped the initial ADT target of 50 ng/dL to 20 ng/dL.

When and how currently available ADT drugs reach their targets, however, varies. With different mechanisms of action, various forms of ADT, which today might more accurately be called androgen targeting therapy, exert different effects on serum FSH and testosterone over time. With bilateral orchiectomy, FSH and testosterone levels immediately fall, but FSH ultimately rises. Conversely, diethylstilbestrol (DES) decreases both testosterone and FSH in the short and long term, although DES was removed from the U.S. market due to cardiovascular toxicity.

GnRH/LHRH receptor agonists bind to and ultimately inhibit LHRH receptors in the anterior pituitary. As with testosterone and LH, the impact on FSH includes, for most patients, a transient surge (up to 300% of baseline) 1-2 days after administration. FSH then decreases by around 70% over the next few weeks to months, followed by steady post-nadir increases that can result in long-term levels 10%-20% below baseline.

Patients on GnRH agonists can take several weeks to achieve LH, FSH and testosterone suppression. As the only G-protein coupled receptor known to lack carboxy-terminal tails, which are crucial for the desensitization process, it takes GnRH/LHRH receptors exceptionally long to respond to chronic agonist administration. Meanwhile, the supraphysiological receptor activation initially provoked by GnRH agonists produces surges in LH, FSH and testosterone that can result in flare symptoms such as acute spinal cord compression, bone pain and ureteral/urethral obstruction.

To reduce flare symptoms, physicians commonly prescribe antiandrogens such as bicalutamide, flutamide or nilutamide with GnRH agonists. But surges still occur during the initial stages of treatment, and testosterone microsurges occur in approximately 6% of patients, particularly with readministration of certain GnRH agonist formulations every 3 or 4 months. FSH flare also occurs.

Recent research shows that due to clinical challenges such as insurance rules, 26.9% of GnRH agonist administrations actually occur late. Late administrations yielded ineffective castration more than 40% of the time, yet clinicians assessed testosterone before GnRH agonist administration only 13% of the time.

Unlike GnRH agonists, GnRH antagonists directly block the GnRH/LHRH receptor, producing immediate and sustained suppression of FSH, LH and testosterone — without surges. Phase 3 research for the GnRH antagonist degarelix included an FDA-mandated crossover trial (CS21A) in which patients initially randomized to the GnRH agonist leuprolide for 1 year switched to the GnRH antagonist degarelix. After 3 months, median FSH in these patients fell 63%, to a level similar to that observed in patients who underwent continuous degarelix treatment. CS21A also showed that PSA failure was 34% lower with degarelix than leuprolide (p = 0.05), and PSA PFS improved significantly in patients who switched from leuprolide to degarelix (HR of 0.20 on leuprolide fell to 0.08 during degarelix extension, p = 0.003), Figure 1.

ADT and cardiovascular risk
Cardiovascular and other comorbidities partly driven by FSH are known to accompany long-term ADT.
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Compared to men without prostate cancer, men with prostate cancer have a higher baseline risk of CV events (more than 2%).\textsuperscript{31} During long-term ADT, FSH can promote development — or exacerbate progression — of atherosclerotic plaques, metabolic syndrome and insulin resistance.\textsuperscript{42}

CV events in particular can happen quickly. A Swedish National Healthcare Registry study by O’Farrell et al showed that in men on ADT, CV events tended to happen within the first 6-12 months of therapy, particularly in patients who had two or more cardiovascular events before initiating ADT (CV event HR 1.2 for men on GnRH agonists).\textsuperscript{43} The same authors noted that in observational studies, GnRH agonists carry consistent increased CVD risk (1.24-2.38 relative risk/RR).

Accumulating clinical data, mainly from observational trials, link ADT with an increased risk for cardiovascular morbidity and mortality. However, retrospective analyses performed on randomized trials have not unequivocally supported a link between ADT and cardiac death.\textsuperscript{43,44}

Even in men without established cardiovascular risk factors, ADT can foster dose-dependent development of metabolic problems such as glucose intolerance, dyslipidemia and increased adiposity.\textsuperscript{45} This increased cardiovascular risk was once considered a byproduct of ADT-induced hypogonadism. However, more recent data highlighting potential differences in cardiovascular risk between many GnRH agonists and antagonists instead implicate a possible ligand-specific mechanism such as T-lymphocyte or cardiac GnRH/LHRH receptor activation, as well as the effect of FSH in mediating cardiovascular effects.\textsuperscript{41}

Differential cardiovascular risks

Due to their differing mechanisms of action, GnRH antagonists may carry a lower risk of CV side effects than do GnRH agonists. Albertsen et al analyzed six Phase 3 trials and found that compared to a total of 837 men on goserelin or leuprolide, 1491 degarelix-treated men had an overall hazard ratio of 0.6, or a 40% reduction in risk of CV event or death during the first year of ADT. Additionally, degarelix-treated men with pre-existing CVD had an HR of 0.44 for CV event or death, and an absolute risk reduction of 8.2%.\textsuperscript{46} These authors suggested that ADT may be an independent risk factor for CV events because activation of T cells to the Th1 phenotype destabilizes atherosclerotic plaques; however, GnRH antagonists appear to halve CV event risk in men with pre-existing CVD compared to GnRH agonists.

In the first prospective study to test cardiovascular outcomes among men with prostate cancer receiving ADT, Margel et al observed no difference in endothelial function (primary outcome) in 39 patients using GnRH agonists versus 41 using GnRH antagonists. However, patients treated with GnRH agonists had significantly more major adverse cardiovascular and cerebrovascular events (MACCE, secondary outcome) compared to those on GnRH antagonists (20% versus 3%, respectively, p = 0.013). Absolute MACCE risk reduction at 12 months for patients using GnRH antagonists was 18% (95% CI: 5%-31%, p = 0.032). “These results suggest that in prostate cancer patients with pre-existing CVD, the selection of ADT modality may differentially affect cardiac outcomes,” these authors wrote.\textsuperscript{47} However, this is a randomized phase 2 trial, and larger studies are needed to confirm this hypothesis.

In an earlier publication by Margel et al, 28% of patients randomized to GnRH agonist ADT experienced a CV event, versus 7% of those randomized to a GnRH antagonist (log rank p = 0.008), at a median follow up of 10 months. Baseline levels of the cardiac biomarker serum NT-proBNP were able to predict CV events, and patients with a less than 60% decrease in FSH levels during the first 3 months of treatment had a higher risk of developing a CV event (40% versus 10%, p = 0.005).\textsuperscript{48}

The differing effects of GnRH agonists and antagonists on FSH levels may explain the differing effects of these agents on the development of atherosclerosis.\textsuperscript{42} In short, GnRH antagonists rapidly decrease FSH to less than 90% of normal levels, while GnRH agonists induce an initial FSH surge followed by gradual decrease to approximately 50% of normal.\textsuperscript{32} With bilateral orchiectomy, by contrast, the loss of Sertoli cells’ inhibitory secretion eventually results in very high FSH levels.\textsuperscript{49}

Zareba et al posited that hyperglycemia, dyslipidemia, central adiposity and sedentary lifestyles contribute to atherosclerotic plaque development, and that increased FSH and decreased testosterone may provoke the local inflammatory process that leads to plaque progression and rupture.\textsuperscript{30} FSH also may contribute to the development of adverse events through its role in formation of reactive oxygen species.\textsuperscript{51}

Multiple authors have outlined a possible receptor-dependent pathophysiology for ADT-induced cardiometabolic problems.\textsuperscript{42,46,50,52} In brief, T cells express GnRH receptors, which are present in atherosclerotic plaque. Activation of these receptors by GnRH agonists can stimulate T cell expansion and differentiation into the proinflammatory Th1 phenotype, which may destabilize atherosclerotic plaques.

Preclinical research supports the potential ligand-dependent impact of ADT on cardiometabolic...
morbidity. In a study of low-density lipoprotein receptor knockout mice treated with GnRH agonists, antagonists or orchietomy for 4 months, those treated with a GnRH antagonist developed less visceral fat and had greater glucose tolerance and smaller atherosclerotic plaques than either castrated mice or those treated with a GnRH agonist.53

Additionally, Liu et al showed that FSH could promote fat storage and lipogenesis in vitro and in vivo.22 In this same study, treating 3T3-L1 pre-adipocytes in mice with FSH accelerated lipid formation, while applying small interfering RNA specific against the FSH receptor reversed this phenomenon. Moreover, giving recombinant FSH to mice treated with a GnRH agonist led to significant weight increase and accumulation of dysfunctional fat, which plays a key role in development of metabolic syndrome and CVD.

Clinical studies have linked ADT with increased fat mass, cholesterol levels and fasting insulin levels, which together seem to mimic metabolic syndrome. However, these changes may not reflect typical metabolic syndrome because studies have shown no increases in blood pressure or inflammatory markers such as C-reactive protein, and the fat increases have been subcutaneous rather than visceral.32 It is also noteworthy that most patients in such studies were probably treated with GnRH agonists, as degarelix was approved in 2008.

PSA nadir levels are associated with improved prognosis.54 GnRH antagonist-driven suppression of testosterone and FSH may lead to improved tumor control, which might delay development of CRPC (measured as PSA failure) versus GnRH agonists.55,56

In a case report, the prolonged survival of an elderly male patient who presented in 2009 with PSA failure 10 years after bilateral orchietomy for Gleason 9 prostate cancer illustrates the importance of FSH control. His PSA had risen to 25 ng/mL, and his testosterone was 35 ng/dL.

After starting degarelix in September 2009, his FSH levels decreased and remained largely undetectable, and his PSA level also became undetectable, while testosterone was < 20 ng/dL. He remained in this remission for 5 years, then died of pneumonia, at which point autopsy revealed only pelvic prostate cancer.57

Altogether, it is plausible that the long-term benefits of GnRH antagonist therapy may accrue, at least partly, to their superior suppression of the FSH system in comparison to GnRH antagonists.6 Studies underway are expected to help address key questions regarding the relationship between ADT and CV event risk:

PRONOUNCE will compare CV safety of degarelix versus leuprolide in patients with advanced prostate cancer and CVD (NCT02663908). Completion is scheduled for 2021.

RADICAL-PC1 & RADICAL-PC2 (NCT03127631) will identify factors associated with development of CVD among men with prostate cancer, focusing on ADT (RADICAL-PC1) and a systematic approach to modifying CV and lifestyle risk factors (RADICAL-PC2). Completion is scheduled for September 2020.

Conclusions

ADT in itself appears to be a risk factor for cardiometabolic comorbidities ranging from myocardial infarction to metabolic syndrome. Evidence suggests that FSH may at least partly drive adverse events such as heart attacks and strokes, perhaps by promoting unfavorable conditions including inflammation, atherosclerosis, insulin resistance, adipocyte rearrangement and plaque instability. The differing effects of GnRH agonists and antagonists on FSH levels during long-term ADT further support the potential contribution of FSH, working through GnRH-receptor dependent mechanisms to promote a pro-inflammatory milieu, to cardiometabolic sequelae. Additional research including prospective, randomized clinical trials is needed to confirm this hypothesis.

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