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ORIGINAL ARTICLE

Prostate Cancer

Follicle-stimulating hormone (FSH) levels prior to prostatectomy are not related to long-term oncologic or cardiovascular outcomes for men with prostate cancer

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Prior research suggests a link between circulating levels of follicle-stimulating hormone (FSH) and prostate cancer outcomes. FSH levels may also explain some of the observed differences in cardiovascular events among men treated with gonadotropin-releasing hormone (GnRH) antagonists compared to GnRH agonists. This study evaluates the association between preoperative FSH and long-term cardiovascular and oncologic outcomes in a cohort of men with long follow-up after radical prostatectomy. We performed a cohort study utilizing an institutional biobank with annotated clinical data. FSH levels were measured from cryopreserved plasma and compared with sex steroids previously measured from the same samples. Differences in oncologic outcomes between tertiles of FSH levels were compared using adjusted cox regression models. Major adverse cardiovascular events (MACE) were similarly assessed using hospital admission diagnostic codes. A total of 492 patients were included, with a median follow-up of 13.1 (interquartile range: 8.9–15.9) years. Dehydroepiandrosterone sulfate (DHEA-S) levels, but not other androgens, negatively correlated with FSH levels on linear regression analysis ($P = 0.03$). There was no association between FSH tertile and outcomes of biochemical recurrence, time to castrate-resistant prostate cancer, or time to metastasis. MACEs were identified in 50 patients (10.2%), with a mean time to first event of 8.8 years. No association with FSH tertile and occurrence of MACE was identified. Our results do not suggest that preoperative FSH levels are significantly associated with oncologic outcomes among prostate cancer patients treated with radical prostatectomy, nor do these levels appear to be predictors of long-term cardiovascular risk.

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INTRODUCTION

Epidemiologic analyses have suggested a link between cardiovascular disease and prostate cancer, with higher rates of cardiovascular disease among patients with prostate cancer than the general population.[1] This may represent an underlying biologic relationship, or the effects of prostate cancer treatment. Androgen deprivation therapy (ADT), and to a lesser degree radiotherapy, for prostate cancer has also been implicated in the risk of cardiovascular events.[2–4] A renewed interest into potential biological reasons emerges with recent reports highlighting a differential effect for patients who are treated with gonadotropin-releasing hormone (GnRH) antagonists compared to traditional GnRH agonists.[5,6]

The suppression of follicle-stimulating hormone (FSH) levels which occurs with GnRH antagonists but not GnRH agonists remains a leading hypothesis to explain large differences in cardiovascular events between these two forms of ADT. Margel *et al.*[5] reported an 18% absolute risk reduction in major cardiovascular and cerebrovascular events one year following ADT initiation with the GnRH antagonist degarelix compared to the GnRH agonist leuprolide. In a trial of 930 patients randomized 2:1 of the oral GnRH antagonist relugolix versus leuprolide, there was a 54% reduction in major adverse cardiovascular events (MACE) among patients who received relugolix relative to patients who received leuprolide.[6] Preclinical studies suggest that FSH may contribute to rupture of unstable atherosclerotic plaques and related cardiovascular events.[7]

A relationship between FSH levels and prostate cancer outcomes has previously been reported. In the CS21 cross-over study of leuprolide and degarelix, patients who crossed over from leuprolide to degarelix experienced more profound suppression of FSH and decreased prostate-specific antigen (PSA) levels.[8] A meta-analysis suggests that suppression of FSH with degarelix following leuprolide may be associated with PSA responses in a minority of patients.[9] Further, serum FSH levels have been reported to predict time to castrate-resistant prostate cancer (CRPC).[10] In localized prostate cancer, preoperative

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elevated FSH levels have been linked to lower testosterone levels and higher grade cancer.[11]

In this study, we sought to examine the relationship between FSH levels and long-term oncologic and cardiovascular outcomes among a cohort of patients treated with radical prostatectomy for localized prostate cancer between 1998 and 2002 using biobanked specimens obtained preoperatively.

PATIENTS AND METHODS

Radical prostatectomy cohort

Institutional ethics approval for this study was obtained from the CHU de Québec-Université Laval (Quebec City, Canada; approval number: #20-2020-4899). We utilized a prospectively accrued institutional cohort and linked biobank to identify 503 patients who underwent a radical prostatectomy at Hotel-Dieu Hospital site of the CHU de Québec network between June 1998 and December 2002, for whom clinical and demographic information was available in our database. This included Charlson comorbidity scores previously recorded based on clinical information at the time of surgery.[12,13]

We sought to examine the relationship between preoperative FSH levels (key exposure) and the primary outcome of cardiovascular events. Secondarily, we considered the relationships between preoperative FSH levels and sex steroid levels, FSH levels and pathologic outcomes (stage and grade), and FSH levels and long-term oncologic outcomes (biochemical recurrence [BCR], metastasis, and CRPC).

Cardiovascular event ascertainment

To obtain information on cardiovascular events, admission administrative codes were obtained from Hotel-Dieu de Québec Hospital as well as the Institut Universitaire Cardiologie et Pneumologie de Québec, both located in Quebec City, Canada. These represent the only two hospital networks providing oncologic or cardiac care in this jurisdiction. The International Classification of Disease (ICD) codes relating to cardiovascular events were identified for all hospital admissions for our cohort of patients following the respective date of surgery. Selection of ICD codes was based on previous published reports,[1,14–16] with MACE defined by the following codes: myocardial infarction (ICD-9-CM code: 410–410.9, ICD-10 code: I21); heart failure (ICD-9-CM code: 428.0–428.10); cerebrovascular accident (CVA; ICD-9-CM code: 430–437, ICD-10 code: I63 and I64); or cardiac shock (CS; ICD-9-CM code: 785.51, ICD-10 code: R5.70).

FSH measurement

Immediately following thawing from −80°C cryostorage, 20 µl of plasma samples was measured for FSH levels using a human enzyme-linked immunosorbent assay (Cayman Chemicals, Ann Arbor, MI, USA) according to the manufacturer's instructions.

Statistical analyses

For statistical analyses, patients were divided into tertiles based on preoperative FSH levels. Relationships between FSH levels and sex steroids were assessed using linear regression analysis. To assess the relationship of FSH tertile on time to BCR, metastases, or CRPC, we used multivariable Cox regression analysis adjusted for baseline PSA, age, and biopsy Gleason grade. BCR was defined as by a PSA ≥0.3 ng ml^{-1} or as salvage radiotherapy due to a rising PSA. The presence of metastasis was defined according to regular follow-up imaging. CRPC was defined by at least 2 rising PSA values or the new appearance of metastases in patients with a castrate testosterone levels. Similarly, Cox regression analyses were used to assess the relationship of FSH tertiles on MACE and death, adjusted for age and preoperative Charlson comorbidity index (CCI). Statistical analyses were performed using Prism version 9.0 (GraphPad Software, San Diego, CA, USA) and R version 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Data were available for a total of 503 patients, with 492 patients having cryopreserved plasma available for FSH measurement. The mean age of the patients was 64.0 years, with a median follow-up of 13.1 years. A total of 336 (68.3%) patients had Gleason Grade group 2 or higher on surgical pathology. The median FSH was 6.10 (interquartile range [IQR]: 4.02–9.49) U l^{-1}. Demographic and clinical characteristics of the cohort are summarized in **Table 1** according to FSH tertile.

With sex steroids previously measured using mass spectroscopy from the same plasma samples,[17] we first sought to assess for relationships between FSH levels and androgens (testosterone, dihydrotestosterone [DHT], dehydroepiandrosterone [DHEA], and DHEA-sulfate [DHEA-S]). We observed that DHEA-S levels negatively correlated with FSH levels on linear regression analysis (**Figure 1a**; $P = 0.03$); no other significant correlations were observed. We also observed that FSH levels correlated with age on linear regression analysis (**Figure 1b**; $P = 0.002$).

The median follow-up of these patients was 13.1 (IQR: 8.9–15.9) years. A total of 151 (30.7%) patients experienced a BCR at a median time of 15.0 months. Multivariable cox regression analysis adjusted for age, baseline PSA, and biopsy Gleason grade found no association between FSH tertile and prostate cancer-related outcomes, including BCR, time to CRPC, or time to metastasis (**Table 2**).

During follow-up, MACEs were identified in 50 (10.2%) patients, with a mean time to first event of 8.8 years. Due to concern regarding capture rate for nononcologic events of patients living remote to the institutions included, we evaluated differences between patients with a postal code in the immediate referral region versus those at a greater distance. This demonstrated that 35/258 (13.6%) patients in the Quebec City region had a MACE during follow-up versus 15/231 (6.5%) patients from outside regions. Therefore, for multivariable analysis assessing for relationships between FSH tertiles and long-term incidence of MACE, we included only the Quebec City population (**Table 3**). In this subpopulation, neither age, tertile of FSH level, nor CCI impacted the risk of MACE. In an analysis of all patients, the CCI did predict risk of MACE (CCI ≥2 *vs* CCI = 0: hazard ratio [HR], 2.34; 95% confidence interval [CI]: 1.11–4.95).

A total of 113 (23.0%) patients died during follow-up, with 15 (3.0%) dying of prostate cancer. For the Quebec City population, age (adjusted HR, 1.05; 95% CI: 1.01–1.09) and CCI (CCI ≥2 *vs* CCI = 0: adjusted HR, 2.76; 95% CI: 1.51–5.02) were significantly associated with overall survival. Similarly, for all patients, both age (adjusted HR,

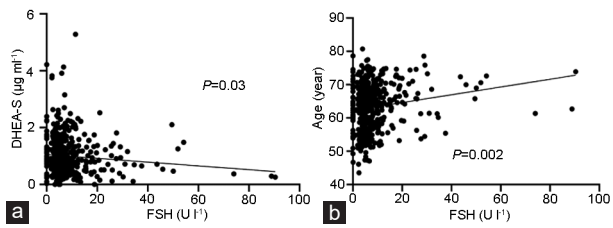

Figure 1: Relationships of DHEA-S and FSH levels from all preoperative plasma samples from a cohort of 492 patients undergoing radical prostatectomy for localized prostate cancer. The slopes for the linear regression between (**a**) DHEA-S and FSH values, as well as (**b**) age and FSH, were significantly non-zero. FSH: follicle-stimulating hormone; DHEA-S: dehydroepiandrosterone-sulfate.

Table 1: Characteristics of patients included in study according to tertile of follicle-stimulating hormone level

Variable	*Lowest tertile (n=164)*	*Middle tertile (n=164)*	*Highest tertile (n=164)*	*All patients (n=492)*	*P*
Age at radical prostatectomy (year), median (IQR)	62.5 (51.5–73.4)	63.4 (52.3–74.4)	65.6 (56.3–74.9)	64.0 (58.2–68.4)	<0.001
Surgical pathology Gleason grade group, *n* (%)					0.34
1	43 (26.2)	56 (34.1)	53 (32.3)	152 (30.9)	
2	58 (35.4)	41 (25.0)	47 (28.7)	146 (29.7)	
3	23 (14.0)	34 (20.7)	29 (17.7)	86 (17.5)	
4	24 (14.6)	17 (10.4)	22 (13.4)	63 (12.8)	
5	15 (9.1)	15 (9.1)	11 (6.7)	41 (8.3)	
Stage, *n* (%)					0.42
pT2	101 (61.6)	104 (63.4)	90 (54.9)	295 (60.0)	
pT3a	42 (25.6)	38 (23.2)	42 (25.6)	122 (24.8)	
pT3b/pT4	20 (12.2)	21 (12.8)	30 (18.3)	71 (14.4)	
Charlson comorbidity index, *n* (%)					0.72
0	114 (69.5)	107 (65.2)	109 (66.5)	330 (67.1)	
1	33 (20.1)	38 (23.2)	32 (19.5)	103 (20.9)	
≥2	16 (9.8)	19 (11.6)	23 (14.0)	58 (11.8)	
Biochemical recurrence, *n* (%)	52 (31.7)	48 (29.3)	51 (31.1)	151 (30.7)	0.85
Developed metastases, *n* (%)	8 (4.9)	8 (4.9)	10 (6.1)	26 (5.3)	0.85
Developed CRPC, *n* (%)	7 (4.3)	4 (2.4)	5 (3.0)	16 (3.3)	0.63
Deceased, *n* (%)					0.52
Prostate cancer related	6 (3.7)	3 (1.8)	6 (3.7)	15 (3.0)	
Other causes	30 (18.2)	34 (20.7)	34 (20.7)	98 (19.9)	
Follow-up (year), median (IQR)	13.8 (8.0–19.7)	13.1 (5.7–20.5)	12.8 (5.4–20.2)	13.1 (9.0–15.9)	

IQR: interquartile range; CRPC: castrate-resistant prostate cancer

Table 2: Association between follicle-stimulating hormone tertile and long-term incidence of surgical and long-term clinical outcomes

Variable	*Lowest FSH tertile, adjusted HR*	*Middle FSH tertile, adjusted HR (95% CI)*	*Highest FSH tertile, adjusted HR (95% CI)*
BCR	1.00	0.92 (0.62–1.36)	1.03 (0.69–1.52)
CRPC	1.00	0.59 (0.17–2.03)	0.86 (0.27–2.73)
Metastasis	1.00	1.11 (0.41–2.99)	1.57 (0.61–4.02)

HR adjusted for age, PSA, and biopsy Gleason score, with 95% CI indicated. FSH: follicle-stimulating hormone; HR: hazard ratio; PSA: prostate-specific antigen; CRPC: castrate-resistant prostate cancer; CI: confidence interval; BCR: biochemical recurrence

Table 3: Association between follicle-stimulating hormone tertile and long-term incidence of major adverse cardiovascular events and overall mortality stratified by residence in the Quebec City region

Variable	*Lowest FSH tertile*	*Middle FSH tertile*	*Highest FSH tertile*
MACE			
n	13	11	11
Adjusted HR (95% CI)	1.00	0.96 (0.50–1.87)	0.80 (0.40–1.59)
Deaths			
n	21	26	31
Adjusted HR (95% CI)	1.00	0.96 (0.61–1.49)	0.97 (0.63–1.49)

HR adjusted for age and baseline Charlson comorbidity index (0, 1, or ≥2), with 95% CI indicated. FSH: follicle-stimulating hormone; MACE: major adverse cardiovascular events; HR: hazard ratio; CI: confidence interval

1.07; 95% CI: 1.04–1.10) and CCI (CCI ≥2 *vs* CCI = 0: adjusted HR, 2.57; 95% CI: 1.59–4.15) predicted overall survival. FSH tertile had no significant impact on survival when the analyses were stratified by Quebec City residence (**Table 3**).

DISCUSSION

Our understanding of the relationship between oncologic and cardiovascular disease continues to evolve. In this study, we evaluated FSH levels preoperative cryopreserved samples from a cohort of radical prostatectomy patients with long follow-up. In contrast to smaller prior reports,[11,18,19] we did not find a significant relationship between preoperative FSH levels and long-term oncologic or cardiovascular outcomes.

Multiple studies now support that lower preoperative testosterone values are associated with an increased risk for adverse pathology among men undergoing radical prostatectomy.[20–23] With feedback increases in FSH physiologically expected with low testosterone values, our null findings were unexpected. We did not observe significant correlations between testosterone or DHT and FSH levels. DHEA-S, the most abundant circulating androgen, was found to correlate negatively with FSH. DHEA-S is also known to decrease with age, which was positively correlated with FSH levels. The variation of the time of day of the blood draw may have introduced more variability in the testosterone results since collection time was not standardized. The older age of our cohort compared to other series may also contribute to our null findings, as prior research suggests the relationship between preoperative androgen levels and surgical pathology findings may decrease with age.[20]

Fewer studies have directly assessed the prognostic importance of circulating FSH levels. A prior study of preoperative FSH levels in 250 men who underwent radical retropubic prostatectomy for prostate cancer reported significantly higher levels of serum FSH in patients with locally advanced prostate cancer as compared with localized cancer (7.07 ± 0.65 U l^{-1} *vs* 5.63 ± 0.31 U l^{-1}).[19] Ide *et al.*[18] reported

an association with preoperative FSH and presence of extraprostatic extension. Porcaro *et al.*[11] reported FSH values preoperatively to be inversely related to total tumor volume and total testosterone in a series of 126 patients. Concordant with another report,[24] our results in a larger cohort do not validate these results.

Our null findings evaluating FSH levels on overall mortality are mirrored by similar studies assessing testosterone on long-term mortality.[25] Whether men undergoing radical prostatectomy have a higher long-term risk of cardiovascular events remains difficult to ascertain from the literature, with a large selection bias expected. As the only center performing radical prostatectomy for the region in a universal health care system, our results may be more representative, but remain biased due to the selection of patients who receive surgery versus radiotherapy. We also note that the cumulative incidence of MACE in our study (10.2%) is comparable to the literature for men of this age.[26]

Our study has several strengths. Our well-characterized cohort has excellent long-term follow-up. The sample size is relatively large and from within a universal health-care system, decreasing the potential for selection bias. The previously reported measurement of sex steroids was performed by a highly-experience laboratory using highly accurate mass spectroscopy methods.[27] Whether there remains a greater effect of FSH levels among patients who received ADT as suggested by prior reports could not be ascertained, given that few patients in our study received ADT.

There are nonetheless limitations to this study. FSH values are based on a single measurement, which occurred within weeks prior to the surgery date. The number of events limits the power to detect significant smaller differences. The use of administrative codes may result in misclassification bias. The use of codes from both the major cancer hospital and the major center for all regional cardiovascular care decreases the possibility of missed events, which nonetheless are possible over time due to migration and loss of follow-up. However, the decreased migration rates in our region help mitigate against these potential problems.

In summary, our results do not suggest that preoperative FSH levels are significantly associated with oncologic outcomes among patients with localized prostate cancer treated with radical prostatectomy, nor do these levels appear to be predictors of long-term incidence of major adverse cardiovascular events. Further research should focus on the importance of FSH levels during ADT among patients with advanced prostate cancer.

AUTHOR CONTRIBUTIONS

PT conceived of the study and provided supervision. KK and PT drafted the manuscript. FHJ performed the immunoassays. CJDW and PT performed the statistical analyses. LL, FD, CG, YF, and HH contributed to the database creation and maintenance. All authors read and approved the final manuscript.

COMPETING INTERESTS

CJDW reports consulting fee from Janssen. PT reports research funding from Bristol-Myers-Squibb, Sanofi, and Janssen as well as personal fee as a consultant from Bayer, TerSera, Janssen, Ferring, and Abbvie. The other authors declared no competing interests.

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