Original Study

Preorchiectomy Leydig Cell Dysfunction in Patients With Testicular Cancer

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Abstract

Leydig cell function was evaluated preorchiectomy in 561 patients with testicular cancer and compared with a cohort of age-matched healthy men. Leydig cell dysfunction was found in 25% of patients and was associated with increasing tumor size. Total testosterone as well as calculated free testosterone was lower in patients than in healthy controls.

Background: Little is known about preorchiectomy Leydig cell function in patients with testicular germ cell cancer (TGCC). The aim was to estimate the prevalence of preorchiectomy Leydig cell dysfunction and evaluate factors associated with this condition in a cohort of patients with TGCC. **Patients and Methods:** We evaluated luteinizing hormone (LH), total testosterone (TT), calculated free T (cFT), estradiol, and sex hormone–binding globulin (SHBG) preorchiectomy in 561 patients with TGCC and compared with 561 healthy controls. We calculated TT/LH and cFT/LH ratios and constructed bivariate charts of TT/LH and cFT/LH from the controls. Logistic regression analysis with an abnormal cFT/LH ratio as outcome and clinical stage, tumor size, age, histology, presence of contralateral germ cell neoplasia in situ (GCNIS), and bilateral tumors as covariates was performed. **Results:** In patients who were negative for human chorionic gonadotropin (hCG) (n = 374), TT ($P = .004$), cFT ($P < .001$), TT/LH ratio ($P = .003$), and cFT/LH ratio ($P = .002$) were lower than in controls. A total of 95 (25%) and 91 (24%) of hCG-negative patients had abnormal values when using combined evaluation of TT/LH and cFT/LH, respectively. Increasing tumor size, contralateral GCNIS, and increasing age were associated with Leydig cell dysfunction. In patients positive for hCG (n = 187), all reproductive hormones except SHBG were different from controls ($P < .001$). **Conclusion:** Patients with TGCC are at increased risk of Leydig cell dysfunction before orchiectomy. Contralateral GCNIS, increasing age, and increasing tumor size are associated with Leydig cell dysfunction. We hypothesize that patients with preexisting Leydig cell dysfunction are at increased risk of testosterone deficiency following treatment.

Clinical Genitourinary Cancer, Vol. ■, No. ■, 1-6

Keywords: Estradiol, Luteinizing hormone, Reproductive hormones, Testicular germ cell cancer, Testosterone

Introduction

Few studies have investigated preorchiectomy Leydig cell function in patients with testicular germ cell cancer (TGCC).[1-3] It has been reported that the serum concentrations of luteinizing hormone (LH) and total testosterone (TT) are similar to those in healthy controls. However, when using combined evaluation of LH and TT, more than 30% of patients with stage I TGCC have Leydig cell dysfunction.[3] This condition is characterized by elevated LH while TT is either normal or reduced. Accordingly, combined evaluation of LH and TT may be a better tool for evaluation of Leydig cell dysfunction than evaluation of either of the hormones alone.[4] Germ cell neoplasia in situ (GCNIS) in the non–tumor-bearing testicle and bilateral tumors are associated with Leydig cell dysfunction.[5,6] Furthermore, systemic inflammation, a general cancer effect,[7] a direct tumor effect[1] and testicular dysgenesis[8] have been proposed as possible factors associated with preorchiectomy Leydig cell dysfunction in patients with TGCC.

Patients with TGCC are treated with orchiectomy and approximately 50% will need additional radiotherapy or chemotherapy for

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Submitted: Apr 21, 2016; Revised: Jun 28, 2016; Accepted: Jul 13, 2016

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1558-7673/$ - see frontmatter
http://dx.doi.org/10.1016/j.clgc.2016.07.006

disseminated disease.[9] These treatments increase the risk of T deficiency.[10] Thus, patients with preexisting Leydig cell dysfunction might carry an increased risk of manifest T deficiency following treatment and will need closer follow-up for early detection and treatment. The aim of the present study was to evaluate the prevalence of preorchiectomy Leydig cell dysfunction and identify factors associated with this condition in a large unselected cohort of patients with TGCC.

Methods

Patients and Controls

We included patients older than 20 years with TGCC treated at Copenhagen University Hospital, Rigshospitalet, from 1993 to 2015. Only patients with serum TT, LH, estradiol, and sex hormone–binding globulin (SHBG) analyzed fewer than 30 days before orchiectomy (n = 598) were eligible for the study. These hormones were evaluated in all patients with TGCC who, preorchiectomy, delivered a semen sample for cryopreservation. Patients in whom preorchiectomy levels of human chorionic gonadotropin (hCG) were not assessable (n = 37) were excluded; thus, 561 men were included in this study. A group of 839 healthy men from the metropolitan area of Copenhagen served as controls. They were chosen without prior knowledge of fertility and body mass index. Further details concerning the controls have previously been described.[4] From the 839 controls, 561 men with comparable median age were selected for comparisons of reproductive hormones (Table 1). As hCG alters the pituitary-Leydig cell axis,[1] patients with hCG elevation (n = 187) were analyzed separately. Hormonal data on a minor group of stage I patients (11 hCG-positive and 61 hCG-negative) were included in a previous publication.[3] Tumor size was measured as the maximal pathological tumor diameter. In patients with bilateral tumors (n = 7), the tumor with the largest diameter was reported. Tumors containing any nonseminoma component were classified as nonseminomas. Seminomas were classified as seminomas irrespective of hCG level. According to national Danish guidelines, a contralateral surgical biopsy was performed in all patients for evaluation of presence of GCNIS. If GCNIS was present, the patients were offered radiotherapy to the affected testicle to prevent development of a new testicular cancer and thereby avoid bilateral orchiectomy.[11]

Hormone Analyses

Serum concentrations of LH were measured by time-resolved immunofluorometric assay (DELFIA; Perkin Elmer, Turku, Finland) with detection limits of 0.05 and 0.06 IU/L, respectively. Intra-assay and interassay coefficients of variation (CV) were below 5% in the LH assay. SHBG was measured using time-resolved immunofluorometric assay (DELFIA; Perkin Elmer) with detection limits of 0.23 nmol/L until 2014. From 2014, SHBG was measured using Access 2 (Beckman Coulter). Intra-assay and interassay CVs were less than 5% for SHBG. Testosterone was measured using radioimmunoassay (Siemens Coat-a-count) until 2014. From 2014, testosterone was measured using Access 2 (Beckman Coulter). Estradiol was measured by radioimmunoassay

Table 1 Characteristics of 561 Patients and 561 Healthy Controls

Outcomes	Patients Negative for hCG	*P*	Patients Positive for hCG	*P*	Controls
Number	374	n/a	187	n/a	561
Age	32 (28-36)	.1	30 (26-36)	.2	30 (27-40)
Histology		n/a		n/a	n/a
Seminoma	266 (71%)		56 (30%)		
Nonseminoma	108 (29%)		131 (70%)		
Contralateral germ cell neoplasia in situ	23 (6%)	n/a	5 (3%)	n/a	n/a
Bilateral tumors	3 (1%)		4 (2%)		
Stage		n/a		n/a	n/a
I	345 (92%)		121 (65%)		
≥II	29 (8%)		66 (35%)		
Tumor size, cm	3.0 (1.8-4.4)	n/a	4.0 (2.7-5.1)	n/a	n/a
Total testosterone (nmol/L)	15.2 (12.0-19.4)	.004	22.4 (16.5-30.2)	<.001	16.5 (13.2-20.6)
Free testosterone (pmol/L)	309 (256-380)	<.001	470 (118-1240)	<.001	343 (275-414)
LH (IU/L)	3.6 (2.6-5.1)	.068	0.46 (0.12-2.46)	<.001	3.3 (2.5-4.5)
Total testosterone/LH	4.5 (2.9-6.5)	.003	46.0 (7.6-233)	<.001	5.1 (3.7-6.7)
Free testosterone/LH	87.8 (59.8-128.4)	.002	1071 (132-5852)	<.001	104.5 (76.6-136.5)
Estradiol (pmol/L)	75 (57-91)	<.001	145 (81-253)	<.001	98 (79-121)
Estradiol/total testosterone	4.7 (3.6-6.4)	<.001	6.5 (4.7-9.1)	.092	6.0 (4.6-7.7)
Estradiol/free testosterone	0.24 (0.18-0.31)	<.001	0.30 (0.22-0.37)	.9	0.29 (0.23-0.37)
SHBG (nmol/L)	33 (25-44)	.9	33 (25-42)	.4	34 (26-42)

Continuous variables are presented as medians with interquartile range and were compared with controls with independent-samples *t*-test. LH, Total testosterone/LH, Free testosterone/LH, estradiol/total testosterone, estradiol/free testosterone were ln-transformed.
Abbreviations: hCG = human chorionic gonadotropin; LH = luteinizing hormone; SHBG = sex hormone–binding globulin.