Sex Hormone-Binding Globulin is an Independent Predictor of Biochemical Recurrence After Radical Prostatectomy

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Abbreviations and Acronyms

BCR = biochemical recurrence
FSH = follicle-stimulating hormone
FT = free testosterone
LH = luteinizing hormone
PCa = prostate cancer
PSA = prostate specific antigen
RP = radical prostatectomy
SHBG = sex hormone-binding globulin

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Purpose: We studied the association of serum sex hormone levels with clinicopathological variables and biochemical recurrence in men with prostate cancer treated with radical prostatectomy.

Materials and Methods: We prospectively studied preoperative serum sex hormone-binding globulin, luteinizing hormone, follicle-stimulating hormone, and free and total testosterone in 372 patients undergoing radical prostatectomy. Biochemical recurrence was analyzed in 285 patients and defined as prostate specific antigen 0.2 ng/ml or higher at least 30 days after radical prostatectomy. Median followup was 43.6 months.

Results: Median sex hormone-binding globulin was 37.4 nmol/l, luteinizing hormone 4.1 mU/ml, follicle-stimulating hormone 5.9 mU/ml, and free and total testosterone 0.069 and 3.7 ng/ml, respectively. There was no significant association of sex hormone-binding globulin, luteinizing hormone, follicle-stimulating hormone or total testosterone with T and N stage, and margin status. Luteinizing hormone, follicle-stimulating hormone, and free and total testosterone were not associated with biochemical recurrence. In contrast, for each 10 U increase in sex hormone-binding globulin the risk of biochemical recurrence increased by 12% ($p = 0.045$). On multivariable analysis sex hormone-binding globulin achieved independent predictor status after adjusting for standard clinicopathological variables. After stepwise regression a model containing T and N stage, Gleason score, margin status, prostate weight and sex hormone-binding globulin improved the accuracy of a base model by 1.3% (79.0% vs 77.7%).

Conclusions: Preoperative serum sex hormone-binding globulin is independently associated with biochemical recurrence after radical prostatectomy and increases the predictive accuracy of a standard multivariable model. Routine assessment of sex hormone-binding globulin sex hormone-binding globulin may be a helpful adjunct to identify patients who need early adjuvant therapy.

Key Words: prostate; prostatic neoplasms; sex hormone binding globulin; neoplasm recurrence, local; biological markers

Sex hormones such as androgens are crucial for prostate development and maintenance.[1] Studies indicate that sex hormones are involved in PCa development, progression and metastatic spread.[2–4] Since sex hormones can be measured in the serum or plasma of men with PCa, they may represent important biomarkers for diagnosis and monitoring after therapy. In this respect preoperative serum testosterone is associated with PCa T and N stage, Gleason score and BCR after RP.[4–10] However, data are inconsistent

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and testosterone levels are significantly altered by a physiological time of day fluctuation, which hamper its routine clinical use.[11] It is important to identify other sex hormone biomarkers that predict pathological findings and BCR to further enhance the predictive accuracy of standard prognostic variables.

SHBG regulates the bioavailability of sex steroids.[12] SHBG is in part produced and regulated in the prostate as prostatic SHBG mRNA, and an SHBG-like antigen was found.[13] In contrast to testosterone, SHBG does not show a time of day fluctuation and, thus, it may be a more reliable parameter of hormone status.[12] Significantly higher SHBG was found in men with PCa compared with healthy controls. Also, SHBG is associated with PCa lymph node metastasis and extracapsular extension.[14–18] However, to date only sparse data are available on the prognostic significance of SHBG.[19]

We investigated the association of preoperative serum sex hormone levels with clinicopathological variables and BCR in men with PCa treated with RP with particular consideration of SHBG.

PATIENTS AND METHODS

Patient Population

We tested the hypothesis that preoperative serum SHBG, LH, FSH, testosterone and FT are associated with clinicopathological variables and BCR in men with PCa. Sex hormones were measured prospectively in 432 consecutive white European patients treated with open retropubic RP between 2004 and 2007. All patients had an ECOG (Eastern Cooperative Oncology Group) performance status of 0. Patients with liver or thyroid disease, uncontrolled diabetes, hyperprolactinemia, hypoalbuminemia or metabolic syndrome and those who had received neoadjuvant therapy were excluded from analysis. All RPs were done by high volume surgeons (40 or more RPs per year), as defined by Hu et al.[20] A total of 372 patients met study inclusion criteria. The study was approved by the local ethics committee.

Venous blood samples for analysis were drawn after overnight fasting on the day before RP between 8 and 10 a.m. at least 4 weeks after prostate biopsy. Samples were kept at 4C until serum was obtained by centrifugation. Serum aliquots were stored at −80C until final analysis. Sex hormones were measured with electrochemiluminescence immunoassays. FT was calculated by the formula of Vermeulen et al.[21] The lower limit of detection was 0.5 nmol/l for SHBG, 0.1 mU/ml for LH, 0.1 mU/ml for FSH and 0.02 ng/ml for total testosterone. Intra-assay and interassay coefficients of variation were less than 5%, less than 4%, less than 7% and less than 4%, respectively.

Clinicopathological data on each patient were retrieved from the prospectively maintained prostate cancer database at our institution. TNM stage was assigned according to the most recent criteria and Gleason scores were classified by 1 pathologist according to the criteria of the International Society of Urological Pathology.[22,23]

After RP 285 patients were followed with a consistent protocol at our outpatient clinic. According to the protocol PSA was measured every 3 months for the first 5 years and biannually thereafter. Of the 372 patients 87 were excluded from BCR analysis since they were not followed at our outpatient clinic, received immediate postoperative adjuvant radiotherapy or hormonal therapy, or did not attain undetectable PSA. Thus, BCR was analyzed in 285 patients.

Data Analysis

Continuous data are presented as the median and IQR. Categorical data are shown as the number of patients and the percent of the sample. Associations of hormone levels with clinicopathological variables were evaluated with the nonparametric Kruskal-Wallis test and correlations according to Spearman.

The clinical end point of interest was BCR-free survival. BCR was defined as PSA 0.2 ng/ml or higher at least 30 days after RP. BCR-free survival probabilities were estimated using the Kaplan-Meier method and calculated from the date of RP to the date of BCR or last followup. To visualize Kaplan-Meier estimates sex hormone cutoffs were identified by recursive partitioning based survival tree analysis. Univariable Cox proportional hazards models were constructed to address the relative impact of continuous sex hormone levels and clinicopathological variables on BCR-free survival.

Independent predictors of BCR were identified in multivariable Cox models. Certain established clinicopathological prognostic variables were selected as base model predictors of BCR, including PSA, pT and pN stage, margin status, pathological Gleason score and prostate weight. A full multivariable model included the base model and all sex hormone variables (SHBG, LH, FSH, FT and testosterone), which were evaluated as continuous variables. To exclude variables with limited prognostic ability from the full model we used stepwise backward variable selection with the likelihood ratio criterion. This resulted in a reduced model that included T and N stage, pathological Gleason score, positive surgical margins, prostate weight and SHBG. These variables formed the basis of the nomogram.

A nomogram predicting 12 and 48-month BCR-free survival was constructed on the final reduced multivariable model. The nomogram was validated internally by bootstrapping (200 resamples). Calibration plots of the nomogram were created to assess its performance at 12 and 48 months. Predictive accuracy of the base, full and reduced models was assessed by the concordance index. All statistical tests were performed with the R 2.10.1 statistical package (http://cran.r-project.org).

RESULTS

Clinicopathological Variables

Table 1 lists clinicopathological variables and sex hormone levels. There was a positive correlation of patient age with SHBG (ρ= 0.17, p = 0.001), LH