High-Grade Prostate Cancer Is Associated With Low Serum Testosterone Levels

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BACKGROUND. The aim of this study was to assess whether low serum testosterone levels in men with newly diagnosed prostate cancer have an association to the endocrine status, prostate-specific antigen (PSA) levels, Gleason score, and androgen receptor expression.
METHODS. Besides a full clinical work-up, the following hormones were quantified in men with newly diagnosed prostate cancer by serum analysis: total testosterone, human luteinising hormone (hLH), human follicle stimulating hormone (hFSH), estradiol, and dehydroepiandrostendione (DHEA). In a subgroup of men, androgen receptor expression was determined immunohistochemically.
RESULTS. One hundred and fifty six patients (65.7 ± 8.5 yrs) with a mean PSA of 29.8 ng/ml (median: 7.4 ng/ml) were analysed. Fifty-two patients (33%) had a partial androgen deficiency (serum testosterone <3.0 ng/ml). These men had lower hLH (3.3 vs. 5.9 mIU/ml), hFSH (6.2 vs. 8.4 mIU/ml), and estradiol (18.8 vs. 29.1 pg/ml) serum levels. Mean Gleason score was higher (7.4 vs. 6.2) in men with a low serum testosterone, PSA-levels were lower (25.3 vs. 31.9 ng/ml). Mean testosterone levels decreased from 4.1 ± 1.7 ng/ml in patients with Gleason scores ≤ 5 to 2.8 ± 2.7 ng/ml with Gleason scores ≥ 8. Androgen receptor expression was higher in patients with low serum testosterone.
CONCLUSIONS. Patients with high Gleason score prostate cancer have lower testosterone and estradiol serum levels. The fact that gonadotropins were lower in parallel suggests a tumor-mediated suppression of the hypothalamic-pituitary-gonadal hormone axis particularly in men with high Gleason score tumours. *Prostate 47:52–58, 2001.* © 2001 Wiley-Liss, Inc.

KEY WORDS: **prostate cancer; testosterone; estrogen; androgen deficiency; Gleason score**

INTRODUCTION

Prostate cancer results from a complex and yet unclear interaction between aging, genetic factors, hormones, growth factors, and environment [1,2]. Hormones, particularly androgens, are believed to play a key role in the etiology of prostate cancer because they are necessary for growth and maintenance of the prostate gland [1,2]. Androgen action in prostate cancer is mediated through the androgen receptor—a ligand-dependent transcription factor that is a member of the steroid/thyroid hormone receptor gene superfamily [1,2].

The responsiveness of prostate cancer to androgen withdrawal, the observation that men castrated prior to puberty (eunuchs), and individuals with an inherited 5α-reductase deficiency do not develop prostate cancer suggest at least a permissive role of androgens. Based on these observations, a number of prospective, cross-sectional or case-control clinical

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studies have evaluated the potential diagnostic/prognostic value of serum testosterone and free testosterone measurement in prostate cancer patients [3–7]. These studies yielded conflicting data, yet the majority were negative. The second most frequently studied steroid hormone in this respect is oestradiol. Although, in parallel to androgens, conflicting data were reported, a recent prospective study suggests that low estradiol levels represent an additional risk factor for prostate cancer [8].

The relevance of testosterone for the development of clinical prostate cancer is challenged by the fact that testosterone serum levels decrease with age (0.25–0.4%/year) while the incidence of prostate cancer increases in parallel [9,10]. The percentage of men with partial androgen deficiency as defined by total serum testosterone levels of less than 3.0 ng/ml increases with age and is estimated to be in the range of 20% in elderly men [10]. Two recent studies have suggested that a low serum testosterone might be associated with clinical prostate cancer [11,12]. Morgenthaler et al. [11] reported on an unusually high prevalence (14%) of prostate cancer in a group of elderly with partial androgen deficiency and a normal digito-rectal examination and serum prostate-specific antigen (PSA). The authors hypothesised that a low serum testosterone might lower PSA thus making it an unreliable marker in these patients [11]. The same group reported that men with low free testosterone levels had more extensive prostate cancer and a higher percentage of Gleason score 8 or higher prostate cancer [12].

Prompted by these data we performed a comprehensive endocrine study of men with untreated, newly diagnosed prostate cancer. We were interested (i) in the prevalence of low serum testosterone levels in untreated prostate cancer patients and (ii) the association of hypoandrogenism to the endocrine status, PSA/free PSA, and Gleason score in men with prostate cancer.

MATERIAL AND METHODS

Patients

Between January 1999 and April 2000, men (Caucasian only) with newly diagnosed, untreated prostate cancer seen at the Department of Urology, University of Vienna, were included to this study. None of the men included in this study were taking any medication (e.g., finasteride) affecting serum hormone levels. The diagnosis of prostate cancer was made by transrectal ultrasound guided octant biopsies in all patients (six biopsies were taken from the peripheral zone and two of the transition zone) [13]. The indication for prostate biopsy was either a suspicious finding on digital rectal examination (DRE) and/or elevated serum PSA (equimolar AxSYM PSA assay, Abbott Laboratories, USA) concentrations using age-specific reference values: 40–49 yrs: <2.5 ng/ml; 50–59 yrs: <3.5 ng/ml; 60–69 yrs: <4.5 ng/ml, 70+ yrs: <6.5 ng/ml. Further diagnostic work-up included a nuclear bone scan and assessment of prostate volume by transrectal ultrasound. Patients taking any medication with a known effect on the endocrine system (e.g., finasteride) were excluded from the current study. We would like to emphasise that none of the patients had ever received any form of antiandrogen therapy prior to study entry.

The Gleason score was determined by a pathologist (A.H.) specialised in prostate diseases [14]. In patients who underwent radical prostatectomy, the Gleason score was determined on the surgical specimen, in the remaining cases on prostate biopsy samples. The pathologist was blinded to the results of the endocrine studies.

Endocrine Study

Serum samples for the endocrine study were obtained by cubital vein puncture of fasting patients between 7:30–10:00 AM prior to any intervention. The following hormones were quantified by commercially available immunoassays (the respective inter- and intra-assay coefficients of variation are given in brackets): dehydroepiandrostendione-sulphate (DHEAS, Spectrica Coated Tube Radioimmunoassay by Orion Diagnostica, Espoo, Finland; normal range: 0.38–4.13 μg/ml) [4.5%/2.0%]; human luteinising hormone (hLH), [4.5%/2.0%]; (normal range: 1–9 mIU/ml), human follicle stimulating hormone (hFSH), [4.3%/3.2%]; (normal range: 1–8 mIU/ml) and estradiol [5.6%/2.6%]; (normal range: 14–60 pg/ml) were quantified by automated fluorescence polarization assays on AxSYM (Abbott Laboratories, Chicago, USA). Testosterone [8.9%/5.2%]; (normal range: 2.7–10.7 ng/ml) was determined by a coat-a-count radioimmunoassay (Diagnostics Products Corporation, Los Angeles, USA).

Immunohistochemistry

Immunohistochemical analysis was done on prostate biopsy specimens of 18 patients, 9 of these patients had serum testosterone values <3.0 ng/ml and 9 had normal total testosterone values. After fixation with formalin tissue was embedded in paraffin. Sections 3-μm thick were dewaxed, rehydrated in alcohol, and immersed in methanol with 0.6% hydrogen peroxidase for 15 min to block endogenous peroxidase activity. After heating the slides for 20 min in a microwave oven at 120 W and three times for 5 min at 600 W, the sections were incubated with the primary

monoclonal Anti-Human Androgen Receptor antibody (AR441, DAKO, Carpinteria, CA) diluted 1:100 at room temperature for one hour. Bound antibody was detected by the avidin-biotin-complex (ABC) peroxidase method (ABC Elite Kit, Vector Laboratories, Burlingame, CA). As a chromogen, 3,3'diaminobenzidine was used. Tissues were counterstained with Mayer's hematoxylin solution. Negative control slides were prepared by omitting the primary antibody. Only nuclear staining was rated positive. A minimum of 300 tumor cells were counted using an integration grid and the percentage of positive nuclei was scored as follows: 0: $<10\%$; 1: $\geq 10\%-<40\%$); 2: $\geq 40\%-<80\%$; 3: $\geq 80\%$. Staining intensity did not vary, therefore we did not consider intensity in our scoring system.

Statistical Analysis

Comparisons of clinical and endocrine parameters as well as androgen receptor expression in patients with low versus normal total serum testosterone values were performed by the Student *t*-test. The correlation of Gleason score to clinical and endocrine parameters were calculated with the Spearman rank correlation test. A *P*-value of <0.05 was considered statistically significant.

RESULTS

Clinical Data

One hundred fifty-six men (65.7 ± 8.5 yrs; mean $\pm$ standard deviation [SD]) were included to this analysis. Principal patient characteristics are given in Table I. Serum total PSA averaged at 29.8 ± 101.6 ng/ml (median: 7.4 ng/ml) (Table II). The mean Gleason score was 6.6 ± 1.5; 11 men (75%) had Gleason scores of seven or less (Table II). Eighteen patients (11.5%) presented with primary metastatic disease (Table I). Mean prostate volume as determined by TRUS was 45.3 ± 22.7 ml. Primary therapy was radical prostatectomy in 102 (65.4%), irradiation in 11 (7.1%), and androgen deprivation therapy in 43 (27.5%) patients.

TABLE I. Patient Demographics

Age	
≤ 50 years	n = 4 (2.6%)
51–60 years	n = 47 (30.1%)
61–70 years	n = 55 (35.3%)
>70 years	n = 50 (32.0%)
PSA	
0–10.0 ng/ml	n = 98 (62.8%)
10.1–20.0 ng/ml	n = 27 (17.3%)
20.1–100 ng/ml	n = 21 (13.5%)
>100 ng/ml	n = 10 (6.4%)
Gleason score	
≤ 5	n = 34 (21.8%)
6	n = 33 (21.2%)
7	n = 51 (32.7%)
≥ 8	n = 38 (24.3%)
Pathological staging (in patients undergoing radical prostatectomy; n = 102)	
pT2	n = 43 (42.2%)
pT3	n = 52 (51.0%)
pT4	n = 7 (6.8%)
Primary metastatic disease	
No	n = 138 (88.5%)
Yes	n = 18 (11.5%)

TABLE II. Principal Clinical Characteristics and Comparison of Individuals With a Partial Androgen Deficiency Versus Normal Values*

	Total n = 156	Te[a] <3.0 ng/ml n = 52	Te ≥ 3.0 ng/ml n = 104	*P*-value[b]
Age (years)	65.7 ± 8.5	66.5 ± 9.0	64.8 ± 8.2	n.s.
PSA (ng/ml)	29.8 ± 101.6	25.3 ± 51.3	31.9 ± 119.2	n.s.
fPSA (%)	17.4 ± 10.7	17.6 ± 12.4	17.3 ± 10.1	n.s.
Estradiol (pg/ml)	25.7 ± 13.4	18.8 ± 11.3	29.1 ± 13.0	0.0001
Testosterone (ng/ml)	3.7 ± 2.3	1.3 ± 1.1	4.8 ± 1.8	0.0001
DHEA-S (μg/dl)	1.3 ± 0.9	1.2 ± 1.0	1.3 ± 0.8	n.s
hFSH (mIU/ml)	7.7 ± 5.8	6.2 ± 4.6	8.4 ± 6.2	0.02
hLH (mIU/ml)	5.0 ± 5.2	3.3 ± 6.0	5.9 ± 4.5	0.004
Gleason score	6.6 ± 1.5	7.4 ± 1.2	6.2 ± 1.4	0.001
Prostate volume (ml)	45.3 ± 22.7	45.7 ± 25.4	45.1 ± 21.6	n.s.

*Mean $\pm$ SD are given.
[a]Total serum testosterone.
[b]The *P*-value indicates the difference between individuals with low versus normal serum total testosterone values. n.s., not significant.

Endocrine Data

Mean endocrine levels of total testosterone, hLH, hFSH, estradiol, and DHEA-S were consistently within the age-specific reference values (Table II). In parallel to Morgenthaler et al. [11] and Hoffman et al. [12], patients with a serum total testosterone value of <3.0 ng/ml were classified as having ''partial androgen deficiency'' [11,12]. Fifty-two patients (33%) belonged to this group, 22 (14.1%) had testosterone levels between 2.1–3.0 ng/ml, 6 (3.8%) between 1.1–2.0 ng/ml, and 24 (15.4%) had testosterone levels of less than 1.0 ng/ml.

Association of Partial Androgen Deficiency to Endocrine Status and Gleason Score

Table II compares clinical, endocrinological, and the Gleason score of patients with and without partial androgen deficiency. In the androgen deficiency group, mean testosterone serum levels averaged at 1.3 ± 1.1 ng/ml as compared to 4.8 ± 1.8 ng/ml in those with normal testosterone values ($P = 0.0001$) (Table II). Age and prostate volume were identical in both groups, serum PSA was lower in the low testosterone group (25.3 ± 51.3 vs. 31.9 ± 119.2 ng/ml), although this difference was not statistically significant. Prostate cancer patients with a low serum testosterone at diagnosis had significantly lower hLH (3.3 vs. 5.9 mIU/ml; $P = 0.004$), hFSH (6.2 vs. 8.4 mIU/ml; $P = 0.02$), and estradiol (18.8 vs. 29.1pg/ml; $P = 0.0001$) serum levels (Table II). Gleason score, in contrast, was significantly higher in the partial androgen deficiency group (7.4 ± 1.2 vs. 6.2 ± 1.4; $P = 0.001$) (Table II). Figure 1 compares Gleason score in men with normal and decreased serum testosterone levels by using a box-plot analysis.

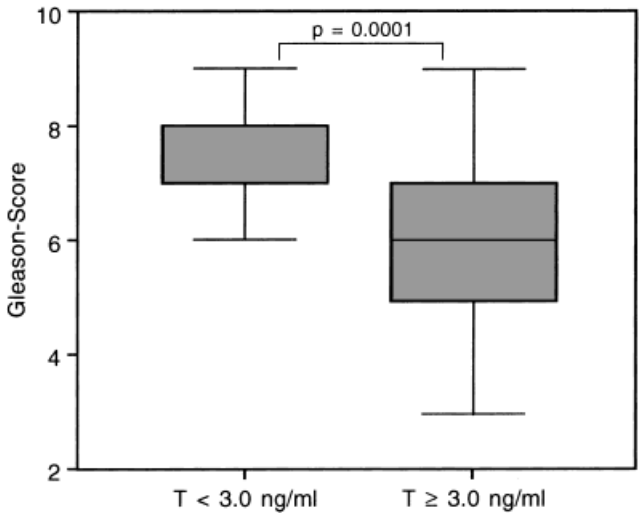

Fig. 1. Comparison of Gleason score in men with normal and decreased (<3.0 ng/ml) testosterone serum levels. Gleason score was significantly higher in men with low (<3.0 ng/ml) testosterone serum levels. The respective ranges (bars) as well as 25, 50, and 75 percentiles, are given.

Similar data were calculated when analysing patients with a PSA <20.0 ng/ml only (Table III). HFSH, hLH, estradiol, and the Gleason score were different in both groups. In this subgroup, the difference of PSA (5.2 vs. 7.7 ng/ml; $P = 0.08$) was at the border of statistical significance (Table III).

Table IV correlates clinical and endocrinological parameters to the Gleason score. Total testosterone ($P < 0.01$) and estradiol ($P < 0.01$) decreased statistical significant with higher Gleason scores. Total testosterone, for instance, decreased from 4.1 ng/ml in men with Gleason scores of 5 or less to 2.8 ng/ml (32% decrease) in those with a Gleason score ≥ 8 (Table IV).

TABLE III. Principal Clinical Characteristics and Comparison of Individuals With a Partial Androgen Deficiency (Total Serum Testosterone <3.0 ng/ml) Versus Those With a Normal Serum Testosterone in Individuals With a Serum PSA <20.0 (ng/ml)*

	Total n = 126	Te[a] <3.0 ng/ml n = 41	Te[a] ≥ 3.0 ng/ml n = 85	P-value[b]
Age (years)	65.4 ± 7.8	66.5 ± 8.2	65.4 ± 7.6	n.s.
PSA (ng/ml)	6.8 ± 4.2	5.2 ± 4.3	7.7 ± 4.1	n.s.
fPSA (%)	17.5 ± 10.4	18.2 ± 12.6	17.2 ± 9.5	n.s.
Estradiol (pg/ml)	26.0 ± 13.9	19.3 ± 12.1	29.2 ± 13.7	0.0001
Testosterone (ng/ml)	3.8 ± 2.3	1.4 ± 1.1	4.9 ± 1.8	0.0001
DHEA-S (μg/dl)	1.3 ± 0.8	1.2 ± 0.9	1.3 ± 0.8	n.s
hFSH (mIU/ml)	7.4 ± 5.2	5.4 ± 2.7	8.2 ± 5.9	0.005
hLH (mIU/ml)	4.8 ± 4.5	2.6 ± 3.3	5.8 ± 4.7	0.0001
Gleason score	6.6 ± 1.5	7.2 ± 1.2	6.2 ± 1.3	0.0001
Prostate volume (ml)	41 ± 20	37 ± 15	43 ± 22	n.s.

*Mean $\pm$ SD are given.
[a]Total serum testosterone.
[b]The P-value indicates the difference between individuals with low versus normal serum total testosterone values. n.s., not significant.

TABLE IV. Association Between Gleason Score and Clinical/Endocrinological Parameters*

	Gleason score			
	≤5 n = 34	6 n = 33	7 n = 51	≥8 n = 38
Age (years)	67.5 ± 8.5	64.0 ± 7.7	63.9 ± 7.4	66.6 ± 10.0
PSA (ng/ml)	13.7 ± 22.8	14.2 ± 24.4	33.9 ± 152.0	51.3 ± 102.1**
%free PSA	25.1 ± 13.6	16.6 ± 5.8	13.2 ± 9.5	15.8 ± 8.7
Testosterone (ng/ml)	4.1 ± 1.7	4.3 ± 1.5	3.7 ± 2.6	2.8 ± 2.7**
Estradiol (pg/ml)	28.7 ± 17.3	29.8 ± 11.1	23.5 ± 12.0	22.5 ± 11.5**

*Mean ± SD are given.
**$P < 0.01$.

A similar pattern, yet less pronounced, was observed for estradiol (Table IV). It is noteworthy that age was almost identical in the four Gleason score groups and was therefore not a confounding factor (Table IV). Figure 2 correlates Gleason score to serum testosterone levels in a box-plot analysis.

Pathological tumor staging in men undergoing radical prostatectomy (n = 102) revealed pT2-cancers in 43 (42.2%), pT3 in 52 (51.0%), and pT4 in 7 (6.8%) (Table I). In men with pT2 cancers, 32.4% had low serum testosterone values, this percentage increased to 38.6% in pT3 cancer and was as high as 62.5% in pT4 tumors.

Androgen Receptor Expression

Androgen receptor expression was analysed immunohistochemically on prostate biopsy specimens in 18 patients who were selected on the basis of their total testosterone level, 9 men had low (testosterone <3.0 ng/ml) and 9 had normal serum testosterone levels (Table V). In men with low testosterone serum levels, 6/9 (66.7%) revealed a very strong androgen receptor-positivity (more than 80% of nuclei androgen receptor-positive) while this was the case in only 3/9 (33.3%) in men with normal testosterone levels (Table V).

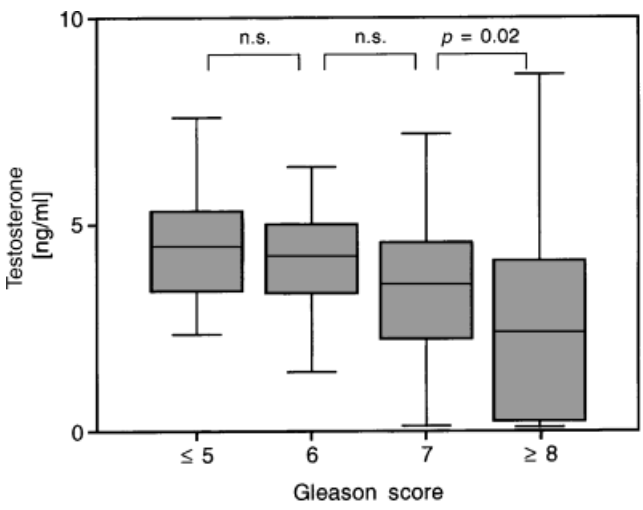

Fig. 2. Association between Gleason score and serum testosterone levels. The respective ranges (bars) as well as 25, 50, and 75% percentiles, are given.

DISCUSSION

The principal findings of this investigation were *(i)* a high prevalence (33%) of partial androgen deficiency in men with newly diagnosed prostate cancer and *(ii)* that individuals with higher Gleason score tumors have lower total testosterone and estrogen serum levels. Hoffman et al. noticed that individuals with low free serum testosterone levels (≤1.5 ng/dl) had more extensive disease and higher Gleason scores [12]. Low serum testosterone values have also been identified as a poor prognostic factor in men with metastatic prostate cancer [15]. Accordingly, Ribeiro et al. [16] observed that patients with metastatic prostate cancer and low serum testosterone had a shorter survival than those with normal testosterone values.

Herein we have additionally analyzed serum gonadotropins, estradiol, and DHEA-S to obtain a more complete insight into the hypothalamic-pituitary-gonadal hormone axis in these individuals. Besides lower serum testosterone levels, patients with high Gleason score prostate cancers additionally had significantly lower hLH, hFSH, and estradiol serum values than patients with normal serum total testosterone. Our group recently compared endocrine patterns in men with newly diagnosed prostate cancer (n = 75) to those with benign prostatic hyperplasia (n = 159) [17]. Men with prostate cancer had lower hLH, hFSH, estradiol, and testosterone serum levels than patients with benign prostatic hyperplasia [17]. 22 (14.1%) of the 156 patients recruited to this study have already been included to this previous analysis

TABLE V. Association Between SerumTestosterone Levels and Androgen Receptor (AR) Expression*

Testosterone	Testosterone (ng/ml)	Estradiol (pg/ml)	PSA (ng/ml)	Gleason score	AR-Receptor-pos[a]
<3.0 ng/ml (n = 9)	1.3 ± 0.7	17.8 ± 11.6	14.2 ± 11.8	7.3 ± 1.2	6/9 (66.7%)
≥ 3.0 ng/ml (n = 9)	5.9 ± 1.0	32.2 ± 12.7	17.0 ± 15.8	5.7 ± 1.8	3/9 (33.3%)

*Mean $\pm$ SD are given.
[a]More than 80% of nuclei androgen-receptor positive.

[17]. These data demonstrate a gradual decrease of hLH, hFSH, estradiol, and testosterone serum levels in the following three groups: (i) benign prostatic hyperplasia; (ii) prostate cancer with lower Gleason scores; and (iii) those with high Gleason score cancers [17].

Prostate cancer patients with an androgen deficiency had lower PSA-values than those with normal serum testosterone despite the fact that the Gleason score in this group was significantly higher (Tables II and III). These findings suggest that PSA-secretion is reduced in men with androgen deficiency. Similar conclusions were drawn by Morgenthaler et al. [11] who observed a high prevalence (14%) of biopsy-proven prostate cancer in men with low total or free testosterone levels despite normal PSA-values and normal digito-rectal examination. The 14% prevalence of prostate cancer in this group is several-fold higher than would be expected for a group with normal PSA levels and DRE results, suggesting that some men in this group might have demonstrated an elevated PSA level or abnormal DRE finding with full androgenic stimulation [11].

In recent years, age-related changes of androgens and, to a lesser extent, of estrogens in elderly men became an area of interest, as these changes have been linked to a number of diseases frequently present in aging men, such as osteoporosis, erectile dysfunction, and a decrease in body/muscle mass [9,10]. Unlike women, no discontinuity occurs in the reproductive life of men, and the respective endocrine changes are more subtle [9,10]. The mechanisms leading to the age-related decline of testosterone and free testosterone are not fully understood yet involve most likely all levels of the hypothalamic-pituitary-gonadal hormone axis, predominantly at the testicular level [10]. The lower basal total testosterone levels may originate from primary testicular changes as suggested by a decreased Leydig cell number, an impaired testicular perfusion and a reduced release of testosterone upon stimulation by hCG [10]. Besides the decrease of testosterone/free testosterone, there is a constant increase of immunoreactive luteinising hormone (hLH) with age in man. On the level of the pituitary gland ageing men have a decrease of the hLH pulse amplitude and mainly a marked decrease of the number of hLH pulses with large amplitude. In addition, the hLH amplitudes in ageing men are inadequately low regarding the decreased androgen levels and a decline of bioactive LH levels has been described [10].

Approximately 20% of elderly men have a partial androgen deficiency, this percentage increases constantly with age: 16.2% (40–49 years), 20% (50–59 years), 22.6% (60–69 years), and 26% (80 years or older) [10]. In prostate cancer patients, the respective percentage were higher in all age groups: 50–59 years, 29.5%; 60–69 years, 30.3%; 70–79 years, 38.8% and ≥ 80 years, 42.9%.

What are the mechanisms leading to the endocrine changes in men with prostate cancer? Most likely, the prostate and particularly prostate cancer cells secrete proteins, which exert a negative feed back on hypothalamic-pituitary-gonadal hormone axis. Miller et al. [18] studied the impact of radical prostatectomy on the hypothalamic-pituitary-gonadal hormone axis in 63 men. Following radical prostatectomy, there was a statistically significant increase in serum total testosterone, free testosterone, estradiol, hLH, and hFSH [18]. The fact that these endocrine changes are not seen after simple prostatectomy, suggest that these factors may be produced by prostate cancer cells [19].

The role of estrogens in the pathogenesis of prostate cancer is poorly understood. Although several controversial publications on this issue are available, a recent large prospective study concluded that low estradiol levels may represent an additional risk factor [8]. Our group has also observed that prostate cancer patients had lower serum estradiol levels than BPH-patients and that these levels further decreased in individuals high grade prostate cancer and low serum testosterone levels (Tables II and III) [17]. Immunohistochemical studies have proven the presence of estrogen receptors in malignant prostatic tissue and Carruba et al. [20] have demonstrated that estrogens exert a cytotoxic effect on hormone-nonresponsive PC3 human prostate cancer cells. The principal source of estrogens in men is the aromatization of androgens to estrogens predominantly in fatty tissue.

CONCLUSION

One-third of men with newly diagnosed prostate cancer have a partial androgen deficiency as defined by serum total testosterone levels of <3.0 ng/ml. These men had also lower hLH, hFSH, and estradiol serum levels as compared to those with prostate cancer and normal testosterone values. Surprisingly, men with a partial androgen deficiency had higher Gleason score tumors than those without testosterone deficiency. These findings suggest a tumor-mediated suppression of the hypothalamic-pituitary-gonadal hormone axis in men with high Gleason score prostate cancer as these patients have additionally suppressed hLH, hFSH, and estradiol levels.

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