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·Original Article·

Serum measurements of testosterone, insulin-like growth factor 1, and insulin-like growth factor binding protein-3 in the diagnosis of prostate cancer among Korean men

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Abstract

Aim: To investigate the relationships of serum testosterone, insulin-like growth factor (IGF)-1 and IGF-binding protein (IGFBP)-3 levels with prostate cancer risk and also with known prognostic parameters of prostate cancer in Korean men who received radical retropubic prostatectomy (RRP) for clinically-localized prostate cancer. **Methods:** Serum levels of total testosterone, free testosterone, IGF-1 and IGFBP-3 were determined in 592 patients who subsequently received prostate biopsy. Results were compared between patients who eventually received RRP for prostate cancer (n = 159) and those who were not diagnosed with prostate cancer from biopsy (control group, n = 433). Among the prostate cancer only patients, serum hormonal levels obtained were analyzed in relation to serum prostate specific antigen (PSA), pathological T stage and pathological Gleason score. **Results:** Prostate cancer patients and the control group demonstrated no significant differences regarding serum levels of total testosterone, free testosterone, IGF-1 and IGFBP-3 across the different age groups. Among the cancer only patients, no significant associations were observed for serum levels of total testosterone, free testosterone, IGF-1 and IGFBP-3 levels with pathological T stage, pathological Gleason score and preoperative PSA. **Conclusion:** Our data indicate that simple quantifications of serum testosterone and IGF-1 along with IGFBP-3 levels might not provide useful clinical information in the diagnosis of clinically localized prostate cancer in Korean men. Also, our results suggest that serum levels of testosterone, IGF-1 and IGFBP-3 might not be significantly associated with known prognostic factors of clinically localized prostate cancer in Korean men. *(Asian J Androl 2008 Mar; 10: 207–213)*

Keywords: prostate; prostate cancer; testosterone; insulin-like growth factor; insulin-like growth factor-binding protein-3

1 Introduction

Prostate cancer is one of the most common male cancers in developed countries. Meanwhile, in Asia where the risk of prostate cancer has previously been known to be much lower, prostate cancer incidence is currently rising rapidly [1]. Factors responsible for such dramatic change might include aging population, westernization of lifestyle, and certainly widespread usage of prostate-specific antigen (PSA) testing. Still, huge differences exist in prostate cancer incidences among Asian and developed countries. Such phenomenon might be a result of an interaction of genetic and environmental factors, which in turn would affect hormonal milieu. As racial variations in the levels of various hormones have been re-

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ported to exist, the significances of hormonal system markers regarding prostate cancer might also be different for those in Asian and developed countries [2, 3].

After observations that certain hormones, such as testosterone and insulin-like growth factor-1 (IGF-1), can affect prostate cancer cell growth, several researchers have investigated the significances of these hormones regarding risk and/or prognosis of prostate cancer in European and American. Certainly, the responsiveness of prostate cancer to hormonal therapy supports the view that testosterone might indeed play an important role in the pathogenesis of prostate cancer. However, conflicting results are reported on the potential diagnostic and/or prognostic value of serum testosterone. As for IGF axis, inconsistent data have also been reported on its value in assessing biological risk and/or prognosis for prostate cancer. Meanwhile, a paucity of published data exists on the significances of serum testosterone, IGF-1 and IGF-binding protein (IGFBP)-3 levels regarding risk and prognosis of prostate cancer in Asian men. Therefore, we investigated the relationship of serum testosterone, IGF-1 and IGFBP-3 levels with prostate cancer risk and also with known prognostic parameters of prostate cancer in Korean men who received radical retropubic prostatectomy (RRP) for clinically-localized prostate cancer.

2 Materials and methods

2.1 Study design

This was a single institutional prospective study performed with upon approval from our institutional review board. Between May 2005 and June 2006, 616 consecutive patients with high serum PSA level (≥ 3.0 ng/mL), a suspicious digital rectal exam, and/or hypoechoic lesion observed via transrectal ultrasound who were evaluated at our department were recruited. To be eligible for enrolment in our study, patients had to have Eastern Cooperative Oncology Group-performance status of one or less and no other medical problem, which might preclude them from having radical prostatectomy if indicated. After obtaining informed consent, blood samples were taken before any prostatic manipulation, and serum levels of total testosterone, free testosterone, IGF-1 and IGFBP-3 were analyzed. All patients subsequently underwent transrectal ultrasound-guided prostate biopsy with at least 12 cores taken.

2.2 Subjects

Of the 616 patients, 183 (29.7%) were diagnosed with prostate cancer from biopsy. Of the 183 cancer patients, 159 eventually underwent RRP for clinically-localized prostate cancer without receiving any hormonal or radiation treatment preoperatively. Among the patients diagnosed with prostate cancer from biopsy, we only included these 159 patients who received radical prostatectomy in our analysis because no exact pathologic staging or Gleason score could be obtained without RRP specimen. The radical prostatectomy specimens were processed by whole-mount technique, and examined by a single pathologist at our institution. Meanwhile, 433 patients who were not diagnosed with prostate cancer from biopsy were designated as the control group.

2.3 Hormonal assay

Serum samples for hormonal evaluation were obtained via cubital vein puncture between 7:30 am and 10:00 am prior to prostate biopsy. Blood samples were collected into Z Serum Separation Clot Activator 8 mL tubes, centrifuged (× 1 500 *g*) at room temperature for 7 min, and immediately stored at a temperature of –80ºC in polypropylene cryopreservation vials. The PSA level was determined by immunoradiometric assay using the ^{125}I-PSA IRMA kit (Institute of Isotopes, Budapest, Hungary). The total and free testosterone levels were, respectively, measured by chemiluminescent microparticle immunoassay using Architect Testosterone Reagent kit (Abbott Laboratories, Chicago, IL, USA) and radioimmunoassay using Coat-A-Count Free Testosterone kit (DPC, Los Angeles, CA, USA). Serum IGF-1 and IGFBP-3 were quantified by immunoradiometric assay using IRMA IGF-1 kit (Immunotech, Marseille, France) and IRMA IGFBP-3 kit (Immunotech, Marseille, France), respectively. Each sample was assayed for each analyte in duplicate, and the average of two values was taken for analysis. Coefficient of variation was less than 8% for each assay.

2.4 Statistical analysis

The SPSS software package version 11.0 (SPSS, Chicago, IL, USA) was used for statistical analysis. Differences in two groups of subjects regarding various parameters were analyzed via Mann-Whitney test. Distributions of categorical variables were compared by χ^2-test. Correlations of continuous variables were analyzed using the Spearman rank procedure. $P < 0.05$ was considered significant.

3 Results

3.1 Baseline characteristics

Principal characteristics of prostate cancer patients and control group included in our study are as listed in Table 1. Median ages of prostate cancer patients and control group were 65 years and 64 years, respectively, demonstrating no significant difference ($P = 0.711$). For the two groups, median PSA values were 8.9 ng/mL and 4.9 ng/mL ($P < 0.001$), respectively. Median prostate volumes as determined from transrectal ultrasound were 41.3 mL and 43.5 mL, respectively ($P = 0.358$). Among the cancer patients, the most common pathologic Gleason score assessed from RRP specimens was 7 (in 61.6%), those with ≥ pT3 tumors were 22%, and those with involvement of surgical margin were 21.4%.

3.2 Comparison of prostate cancer patients and control group

As can be seen in Table 2, prostate cancer patients and the control group demonstrated no significant differences regarding serum levels of total testosterone ($P = 0.367$), free testosterone ($P = 0.284$), IGF-1 ($P = 0.542$) and IGFBP-3 ($P = 0.756$) across the different age groups. Serum total and free testosterone levels appeared to decrease with age, but showed no significant correlation with age in both cancer patients and the control group (all P-values > 0.05). Meanwhile, serum IGF-1 and IGFBP-3 also demonstrated trends of having inverse correlations with age in both cancer patients and the control group, but not being statistically significant (all P-values > 0.05). Serum total and free testosterone showed no significant correlation with either serum IGF-1 or IGFBP-3 levels in both cancer patients and the control group (all P-values > 0.05).

3.3 Analysis of prostate cancer patients only

When prostate cancer only patients were divided into the two groups according to testosterone levels (group 1, those with lowest quartile of serum total testosterone level distribution; group 2, the other remaining patients), group 1 consisted of those with serum total testosterone level of 3.4 ng/mL or lower ($n = 39$), whereas group 2 consisted of 120 patients with testosterone levels higher than 3.4 ng/mL (Table 3). The distributions of age ($P = 0.432$), tumor stage ($P = 0.368$), pathologic Gleason

Table 1. Patient characteristics. PSA, prostate specific antigen.

	Prostate cancer patients (n = 159)	Control group (n = 433)	P value
Median age (range) (years)	65 (48–78)	64 (42–78)	0.711
No. age (%)			
≤ 50 years	14 (8.8)	41 (9.5)	
51–60 years	26 (16.4)	97 (22.4)	
61–70 years	100 (62.9)	219 (50.6)	
> 70 years	19 (11.9)	76 (17.5)	
Median PSA (range) (ng/mL)	8.9 (1.5–48.6)	4.9 (2.1–35.3)	< 0.001
No. PSA (ng/mL) (%)			
< 10.0	100 (62.9)	381 (88.0)	
10.1–20.0	39 (25.4)	49 (11.3)	
> 20.1	20 (12.6)	3 (0.7)	
Median prostate volume (range) (mL)	41.3 (15.0–82.5)	43.5 (20.0–85.5)	0.358
No. pathologic Gleason score (%)			–
≤ 6	56 (35.2)	–	
7	98 (61.6)	–	
≥ 8	5 (3.1)	–	
No. pathologic stage (%)			–
T2a	27 (17.0)	–	
T2b	2 (1.3)	–	
T2c	95 (59.7)	–	
≥ T3	35 (22.0)	–	

Table 2. Comparison of serum levels of various hormones between cancer patients and control group across different age groups. IGF-1, insulin-like growth factor; IGFBP-3, insulin-like growth factor-binding protein.

	Prostate cancer patients (n = 159)	Control group (n = 403)	P value
Median total testosterone (range) (ng/mL)	4.4 (1.4–8.9)	4.5 (1.6–9.1)	0.367
≤ 50 years	4.7 (3.9–8.9)	4.8 (2.4–9.1)	
51–60 years	4.5 (1.5–8.5)	4.7 (2.1–8.9)	
61–70 years	4.4 (1.6–7.7)	4.5 (1.8–8.1)	
> 70 years	4.3 (1.4–6.5)	4.3 (1.6–6.9)	
Median free testosterone (range) (pg/mL)	11.0 (1.9–33.7)	13.5 (1.5–31.0)	0.284
≤ 50 years	18.6 (9.9–33.7)	19.4 (8.8–31.0)	
51–60 years	12.9 (1.5–26.7)	17.1 (1.9–29.5)	
61–70 years	10.8 (1.9–25.3)	12.9 (1.9–27.8)	
> 70 years	9.6 (1.0–20.2)	9.4 (1.5–19.7)	
Median IGF-1 (range) (ng/mL)	254.4 (66.9–711.3)	258.9 (59.5–752.8)	0.542
≤ 50 years	345.4 (189.6–711.3)	341.3 (258.3–752.8)	
51–60 years	275.1 (79.6–638.3)	278.5 (66.9–695.8)	
61–70 years	254.0 (88.9–539.6)	255.6 (86.9–644.1)	
> 70 years	224.7 (66.9–390.3)	189.7 (59.5–377.1)	
Median IGFBP-3 (range) (ng/mL)	4 121.2 (1 967.5–6 320.6)	3 966.8 (1 867.5–5 980.6)	0.756
≤ 50 years	4 555.5 (3 457.6–6 278.3)	4 436.3 (2 539.1–5 980.6)	
51–60 years	4 190.7 (1 967.5–6 300.4)	4 296.6 (1 898.5–5 505.9)	
61–70 years	4 144.3 (1 967.5–6 102.9)	3 990.5 (1 990.8–5 820.4)	
> 70 years	3 767.3 (1 967.5–4 351.9)	3 679.1 (1 867.5–5 010.6)	

Table 3. Comparison of two groups of prostate cancer patients stratified by serum total testosterone levels (cut-off = 3.4 ng/mL). PSA, prostate specific antigen.

	Group 1 (n = 39)	Group 2 (n = 120)	P value
Median total testosterone (ng/mL)	2.7	5.0	< 0.001
Median free testosterone (pg/mL)	7.9	13.7	< 0.001
Median age (years)	63	64	0.432
No. 65 or younger (%)	23 (59.0)	66 (55.0)	
No. older than 65 (%)	16 (41.0)	54 (45.0)	
No. T stage (%)			0.368
T1/T2	32 (82.1)	92 (76.7)	
≥ T3	7 (17.9)	28 (23.3)	
No. pathologic Gleason score (%)			0.735
< 7	14 (35.9)	42 (35.0)	
≥ 7	25 (64.1)	78 (65.0)	
Median PSA (ng/mL)	13.1	10.0	0.258
Marginal positivity	8 (23.1)	26 (21.7)	0.378

score (P = 0.735), serum PSA (P = 0.258) and margin positivity (P = 0.387) were not significantly different between the two groups. Meanwhile, serum IGF-1 levels were correlated with IGFBP-3 levels (P < 0.001). As shown in Table 4, there was no significant association between IGF-1 and IGFBP-3, respectively, with PSA levels (P = 0.454, P = 0.737), tumor stage (P = 0.631, P = 0.844), pathological Gleason score (P = 0.585, P = 0.578) and margin positivity (P = 0.733, P = 0.898) among the patients with prostate cancer.

Table 4. Association of serum IGF-1 and IGFBP-3 levels with known prognostic parameters among prostate cancer patients. IGF-1, insulin-like growth factor; IGFBP-3, insulin-like growth factor-binding protein; PSA, prostate specific antigen.

	IGF-1		IGFBP-3	
	Median (range)	*P* value	Median (range)	*P* value
PSA (ng/mL)		0.454		0.737
< 10	265.1 (66.9–611.7)		4 072.1 (1 967.5–6 320.6)	
≥ 10	222.8 (74.4–711.3)		4 119.8 (2 159.6–6 129.2)	
T stage		0.631		0.844
T1/T2	256.3 (73.6–696.7)		4 065.8 (2 100.3–6 320.6)	
≥ T3	244.8 (66.9–711.3)		4 151.1 (1967.5–6 287.5)	
Pathologic Gleason score		0.585		0.578
< 7	266.5 (66.9–711.3)		3 871.5 (1 990.6–6 320.6)	
≥ 7	245.7 (76.5–689.0)		4 216.6 (1 967.5–6 302.8)	
Surgical margin		0.733		0.898
Positive	251.2 (94.6–456.7)		4 121.5 (2 457.9–5 799.6)	
Negative	260.1 (66.9–711.3)		3 933.8 (1 967.5–6 320.6)	

4 Discussion

Significance of testosterone has been discussed in several studies of patients, mostly European and American, with prostate cancer. Iversen *et al.* [4] report that pretreatment low serum testosterone correlates with decreased survival for prostate cancer. Furthermore, Schatzl *et al.* [5, 6] report that low serum testosterone is associated with higher tumor microvessel and androgen receptor density as well as with higher Gleason scores in patients with newly diagnosed prostate cancer. So far, several published reports have indicated that low testosterone levels are associated with poor outcomes for patients with prostate cancer. However, most such reports are based upon studies that include limited numbers of subjects. Zagars *et al.* [7] claim that high rather than low pretreatment serum testosterone significantly correlates with metastatic relapse after radiation treatment for prostate cancer. As in the present study, Fodstad *et al.* [8] report from their study of 370 patients with newly diagnosed stage T1 to T3pN0M0 prostate cancer that no statistically significant association was found for serum values of testosterone with local tumor stage, Gleason score or PSA. Meanwhile, although Teloken *et al.* [9] reported that low serum testosterone is associated with higher risk of positive surgical margins in RRP specimen, low testosterone levels were not observed to be significantly associated with higher Gleason scores or pathological stage. Also, despite the fact that serum testosterone levels appeared to be predictive of local tumor stage in a recent study of 82 Japanese men who received radical prostatectomy, serum testosterone levels actually showed no significant association with serum PSA level, Gleason score or even PSA recurrence rate [10].

As for IGF, a great amount of attention was initially focused on the potential association of IGF axis and prostate cancer primarily because of the published results of prospective studies suggesting a certain relationship between serum IGF-1/IGFBP-3 levels and risk of developing prostate cancer. Mantzoros *et al.* [11] report that elevated serum IGF-1 levels might increase the risk of prostate cancer. Chan *et al.* [12] state that both IGF-1 and IGFBP-3 might predict the risk of developing advanced prostate cancer while not being much use in screening patients for early stage prostate cancer. Oliver *et al.* [13] observed that risk of prostate cancer increased across quartiles of IGF-1 and association of IGF with prostate cancer risk were stronger for advanced cases. By performing meta-regression analysis, Renehan *et al.* [14] found that increased circulating concentration of IGF-1 is associated with increased risk of prostate cancer. In contrast, Woodson *et al.* [15] observed no evidence from a prospective study that would support a causal association between serum IGF-1 or IGFBP-3 and the risk of prostate cancer. Janssen *et al.* [16] show that measurement of serum levels of IGF-1 and/or IGFBP-3 in addition to PSA does not improve the identification of men at high risk of developing early stage prostate cancer. Finne *et al.* [17] quantified IGF-I and IGFBP-3 serum

levels in 665 consecutive men undergoing prostate biopsies and stated that association between serum IGF-1 and prostate cancer risk was not significant. Ismail *et al.* [18] investigated 652 men undergoing prostate biopsies and conclude that serum IGF-1 and IGFBP-3 do not predict the results of prostate biopsy. Marszalek *et al.* [19] report from their study of 156 men with prostate cancer and 271 controls that serum IGF-1 levels do not correlate with serum PSA, Gleason score and number of positive biopsy cores. Despite the fact that these data were obtained from studying European and American, they are in line with results of our study as we also observed that serum IGF-1 and IGFBP-3 levels did not correlate with serum PSA levels, tumor stage and pathologic Gleason score.

Although most previous reports indicate that low serum testosterone might be somehow associated with poor prognosis for prostate cancer, we observed no evidence to support such an idea in the current study of Korean men with prostate cancer. Racial disparity might contribute to this discrepancy. Various investigators have suggested that racial variations in serum levels of hormones, including testosterone along with its derivatives, exist and that hormonal difference might contribute to differences in prostate cancer risks among different races [3]. Some have shown that Asian men have higher serum total testosterone with lower dihydrotestosterone levels than European and American [2]. Furthermore, the fact that available data regarding the significance of testosterone in relation to prostate cancer are inconsistent suggests that serum testosterone level might not be an ideal diagnostic or prognostic marker for prostate cancer irrespective of the actual association of testosterone with prostate cancer's development and/or aggressiveness. Because so many factors, including age, general condition, timing and method of assaying, influence serum total and free testosterone levels, application of such hormonal marker testing to clinical practice might not be ideal. Meanwhile, although serum testosterone level did not demonstrate any significant correlations with known prognostic parameters of prostate cancer in the present study, it would be inappropriate to completely deny the potential significance of testosterone in relation to the development and/or progression of prostate cancer considering the data currently available in the published literature. However, simple assay of total and free testosterone levels might not provide much information, at least for Asian men with prostate cancer, as shown by our data.

As shown in our study, several previous reports indicated that serum levels of IGF-1 and IGFBP-3 do not have significant correlations with known prognostic parameters of prostate cancer [16–19]. This absence of association should not be immediately translated into a belief that IGF axis as a whole is not related to pathogenesis or progression of prostate cancer. The situation might well be different regarding local tissue expression as decreased local expression of IGFBP-3 is associated with higher grade prostate cancers [18]. Another possible explanation for our negative finding might be that normal circulating IGF-1 levels might exert a greater effect on malignant than normal prostatic tissues. Another member of the IGF axis might be a better prognostic marker for prostate cancer: others have reported that serum IGFBP-2, which is the main IGFBP produced by prostate epithelial cells, is inversely associated with prostate cancer aggressiveness and progression [20]. Still, IGF-1 and IGFBP-3 might not be useful clinical parameters in assessing risk or prognoses of prostate cancer in Asian men.

One of the potential limitations of the present study is the makeup of the control group. Despite the fact that all subjects included in the control underwent 12 or more core transrectal ultrasound-guided biopsies and had negative results, the possibility of prostate cancer existence could not be completely excluded in the control group. However, PSA values of the control group were significantly lower compared with cancer patients. Also, because of the short duration of follow-up, we could not assess the impact of hormones studied on long-term prognoses of patients, which we will analyze in future.

Our data indicate that simple quantifications of serum testosterone and IGF-1 along with IGFBP-3 levels might not provide useful clinical information on the diagnosis of clinically localized prostate cancer in Korean men. Also, our results suggest that serum levels of testosterone, IGF-1 and IGFBP-3 might not be significantly associated with known prognostic factors of clinically localized prostate cancer in Korean men.

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