INSULIN-LIKE GROWTH FACTOR-1 AND INSULIN-LIKE GROWTH FACTOR BINDING PROTEIN-3 FOR PROSTATE CANCER DETECTION IN PATIENTS UNDERGOING PROSTATE BIOPSY

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ABSTRACT

Purpose: Laboratory and epidemiological studies suggest that high circulating insulin-like growth factor (IGF)-1 and low IGF binding protein-3 are associated with increased prostate cancer risk. However, the usefulness of serum IGF-1 or IGF binding protein-3 for predicting pathology results in men undergoing prostate biopsy is unclear. We examined the relationships of serum IGF-1, IGF binding protein-3 and the results of prostate biopsy.

Materials and Methods: A total of 652 consecutive patients with elevated serum prostate specific antigen (PSA) or abnormal digital rectal examination who were referred for transrectal ultrasound sextant prostate needle biopsy underwent blood sampling before biopsy. PSA, free PSA, IGF-1 and IGF binding protein-3 were measured. There were 244 men (37.4%) with cancer and 408 controls with benign conditions.

Results: Mean IGF-1 plus or minus SD in the cancer and control groups was 176.1 ± 58.3 and 178.7 ± 54.7 ng./ml., respectively ($p = 0.57$). Mean IGF binding protein-3 in the cancer and control groups was 2,724 ± 647 and 2,673 ± 589 ng./ml., respectively ($p = 0.3$). Adjustment for age and PSA showed significantly lower IGF-1 in cancer cases, while IGF binding protein-3 was not significant. ROC values were significantly higher for free-to-total PSA and PSA than for crude and age adjusted IGF-1 and IGF binding protein-3.

Conclusions: Our data indicate that serum IGF-1 or IGF binding protein-3 does not predict the results of prostate biopsy in men with elevated PSA or abnormal digital rectal examination. This finding implies that while there is evidence that the IGF-1 level is a risk factor for prostate cancer, neither IGF-1 nor IGF binding protein-3 can be used as a tumor marker for this disease.

KEY WORDS: prostate; prostatic neoplasms; tumor markers, biological; insulin-like growth factor; insulin-like growth factor binding protein 3

Insulin-like growth factors (IGFs) are mitogens that have an important role in regulating cell proliferation, differentiation and apoptosis.[1] The effects of IGFs are mediated through type 1 IGF receptor, a tyrosine kinase that shares certain structural similarities with insulin receptor.[1] The availability of free IGFs for interaction with IGF receptor-1 is modulated by IGF binding proteins. IGF binding proteins, especially binding protein-3, have also been reported to have IGF independent effects on cell growth, mainly inhibitory effects.[1] In the plasma greater than 90% of circulating IGF-1 is bound to IGF binding protein-3.[1] The affinity of IGF binding protein-3 for IGF-1 is decreased by proteases that cleave binding proteins and may cause growth by increasing the availability of free IGF-1. Prostate specific antigen (PSA) is a protease that may modulate the activity of IGF-1.[2]

At least a dozen publications have focused on the association of serum IGF-1, IGF binding protein-3 and prostate cancer.[3–16] Initial epidemiological studies, including a case-control study with a large prospective cohort based on a serum bank of 152 patients with prostate cancer and 152 controls, showed a 2.4-fold increased risk of prostate cancer in the highest IGF-1 quartiles. Adjusting for IGF binding protein-3 further strengthened the association, while high serum IGF binding protein-3 was associated with decreased risk.[3] In addition, 2 case-control studies of newly diagnosed patients showed that serum IGF-1 was higher in men with prostate cancer than in controls.[4,5] These results suggest that high serum IGF-1 and low serum IGFBP-3 are risk factors for prostate cancer. Another 2 prospective epidemiological studies confirmed these observations.[6,7] However, nonprospective studies have shown conflicting results with some supporting the association[8–10] and others not supporting it.[11–16]

Serum PSA is a sensitive marker for prostate cancer but its positive predictive value is generally low. Cancer specificity can be improved by measuring the free-to-total PSA ratio.[17] We determined whether measuring serum IGF-1 and IGF binding protein-3 can improve the detection of prostate cancer in patients with elevated serum PSA or abnormal digital rectal examination undergoing transrectal ultrasound guided prostate biopsy.

PATIENTS AND METHODS

Patients. The study included 652 consecutive patients who presented to the Uromed prostate cancer detection clinic between January 1998 and October 1999. Uromed is an outpatient clinic for the early detection of prostate cancer where men undergo transrectal ultrasound guided prostate biopsy.[18] This patient population was referred to our center exclusively by urologists due to elevated total serum PSA or suspicious digital rectal examination. After patients provided informed consent blood samples were obtained before any prostatic manipulation, followed by transrectal ultrasound guided prostate biopsy with a minimum of 6 biopsies.[18] Of the

652 patients 95% underwent sextant biopsies and the number of biopsies was the same in men with and without cancer. All biopsies were examined by a single genitourinary pathologist (L. B.). Of the patients 244 (37.4%) were diagnosed with prostate cancer, while 408 (62.6%) had no invasive cancer and were considered benign controls. Prostate volume was estimated by transrectal ultrasound according to the formula, $\pi/6 \times$ (transverse $\times$ anteroposterior $\times$ cephalocaudal/diameters).

Serum samples and laboratory methods. Before biopsy a clotted blood sample was obtained in all cases to measure PSA, free-to-total PSA, IGF-1 and IGF binding protein-3. After centrifugation the serum was stored at −80C until analysis. IGF-1 and IGF binding protein-3 were analyzed by enzyme-linked immunosorbent assay with reagents. In our previous studies we showed that IGF-1 and IGF binding protein-3 values determined by enzyme-linked immunosorbent assay correlated highly with radioimmunoassay after acid chromatography (Pearson's r = 0.97), intra-assay coefficient of variations were low at less than 9%, and IGF-1 and IGF binding protein-3 were stable after storage at −80 (r = 0.98).[3]

Statistical analysis. ANOVA was used to compare mean age, prostate volume, IGF-1, IGF binding protein-3, PSA and free-to-total PSA in patients with cancer and benign controls. Contingency tables were analyzed using the Fisher exact and chi-square tests. IGF-1 and IGF binding protein-3 were analyzed as continuous variables and in quartiles. Quartile definition was based on the overall population and on benign controls. No significant difference was noted in the quartiles based on the overall population or controls. Therefore, the data are presented according to a quartile distribution of controls. The Pearson correlation coefficient was used to assess the strength of the correlation of IGF-1 with prostate volume in benign controls versus patients with cancer. The OR with the 95% CIs was calculated to assess cancer risk for quartiles 2 to 4 compared with quartile 1.

In addition, IGF-1 and IGF binding protein-3 values were studied in unmatched and age matched fashion. Age matching was done individually using random process of age matched subject selection according to the mean plus or minus SD age ± 1 year.[4] To evaluate the specificity versus sensitivity of IGF-1, IGF binding protein-3, PSA and free-to-total PSA ROC curves were drawn and the AUC was calculated according to the method of Hanley and McNeil. Multivariate analysis was done using logistic regression. Data were analyzed using commercially available software.

RESULTS

Table 1 shows univariate analysis of various parameters and cancer detection. Mean total PSA was significantly higher in the prostate cancer group than in benign controls ($p < 0.00001$), while mean volume and free-to-total PSA were significantly higher in benign controls ($p < 0.00001$). Mean IGF-1 and IGF binding protein-3 were similar in the 2 groups ($p = 0.57$, and 0.3, respectively). Table 1 also shows the mean values of different ratios of IGF-1 and IGF binding protein-3 that have been reported as possible predictors of prostate cancer, such as IGF-1-to-PSA, IGF binding protein-3-to-PSA and IGF binding protein-3-to-IGF-1.[3,12] Statistical significance was noted for IGF-1-to-PSA and IGF binding protein-3-to-PSA with each lower in the prostate cancer than in the control group ($p < 0.00001$). A trend toward significance was observed for IGF binding protein-3-to-IGF-1 ($p = 0.07$).

As expected, serum IGF-1 and IGF binding protein-3 decreased significantly with increasing age ($p < 0.0001$ and 0.007, respectively).[1] Hence, age adjustment was subsequently performed. Table 2 shows mean PSA, free-to-total PSA, IGF-1, IGF binding protein-3 and various IGF-1 ratios after adjusting for age in men with cancer and benign controls. IGF-1 was significantly lower in those with cancer ($p < 0.001$), while mean IGF binding protein-3 did not significantly differ in the 2 groups ($p = 0.3$). After adjusting for age higher serum IGF-1 and IGF binding protein-3 showed an inverse association with cancer risk according to quartiles (OR 0.4, 95% CI 0.2 to 0.7 and OR 0.6, 95% CI 0.4 to 1, respectively, table 3).

We observed a significant positive correlation of IGF-1 with prostate volume in all cases ($p < 0.01$). This correlation was strongest in men without prostate cancer (Pearson r = 0.63 versus 0.3). This volume-IGF-1 relationship was unaffected by IGF binding protein-3. Table 4 shows mean age adjusted IGF-1 and ultrasound determined prostate volume according to PSA less than 4, 4 to 10 and greater than 10 μg./l. In the 3 PSA subgroups IGF-1 was significantly lower in patients with cancer than in benign controls ($p = 0.001$, 0.03 and 0.03, respectively). Mean prostate volume in benign controls was statistically greater than that in patients with cancer ($p = 0.045$, <0.0001 and <0.0001, respectively). Table 5 lists the specificity of PSA, free-to-total PSA, IGF-1, IGF binding protein-3, IGF-1-to-PSA, IGF binding protein-3-to-PSA and IGF binding protein-3-to-IGF-1 at 85%, 90% and 95% sensitivity.

The accuracy of IGF-1 and IGF binding protein-3 for prostate cancer detection was evaluated by ROC analysis. The AUC was 0.51 for IGF-1, 0.52 for IGF binding protein-3, 0.55 for IGF binding protein-3-to-IGF-1, 0.62 for IGF binding protein-3-to-PSA, 0.63 for IGF-1-to-PSA, 0.64 for PSA and 0.76 for free-to-total PSA (see figure). Multivariate analysis revealed statistical significance for PSA, free-to-total PSA, IGF-1-to-PSA and IGF binding protein-

TABLE 1. *IGF-1, IGF binding protein-3, PSA, free-to-total PSA, IGF-1-to-PSA, IGF binding protein-3-to-PSA and IGF binding protein-3-to-IGF-1 in patients with prostate cancer and controls with benign conditions*

	Prostate Ca	Benign	p Value
No. pts.	244	408	
Mean age ± SD	65.2 ± 6.7	62.8 ± 6.2	0.001
Mean vol. ± SD (gm.)	47.9 ± 31.1	70.7 ± 38.6	0.00001
IGF-1 (ng./ml.):			
Mean ± SD	176.1 ± 58.3	178.7 ± 54.7	0.57
Median	175.3	179.5	
IGF binding protein-3 (ng./ml.):			
Mean ± SD	2,724 ± 647	2,673 ± 590	0.3
Median	2,725	2,674	
PSA (ng./ml.):			
Mean ± SD	13.9 ± 31	7.3 ± 7.3	0.00001
Median	7.7	6	
Mean free/total PSA ± SD	14.4 ± 8.7	22 ± 10.2	0.00001
Mean IGF-1/PSA ± SD	27.1 ± 22	54.7 ± 115	0.00001
Mean IGF binding protein-3/PSA ± SD	432 ± 354	828 ± 1,704	0.00001
Mean IGF binding protein-3/IGF-1 ± SD	16.7 ± 6.2	15.9 ± 5.1	0.07

TABLE 2. *Age matched IGF-1, IGF binding protein-3, PSA, free-to-total PSA, IGF-1-to-PSA, IGF binding protein-3-to-PSA and IGF binding protein-3-to-IGF-1 in patients with prostate cancer and controls with benign conditions*

	Prostate Ca	Benign	p Value
No. pts.	231	231	
Mean age ± SD	64.6 ± 6.4	64.5 ± 6.4	0.8
Mean vol. ± SD (gm.)	33.5 ± 30	76.4 ± 33	0.0001
IGF-1 (ng./ml.):			
Mean ± SD	176 ± 58	197 ± 43	0.001
Median	175	190	
IGF binding protein-3 (ng./ml.):			
Mean ± SD	2,732 ± 650	2,789 ± 480	0.3
Median	2,725	2,785	
PSA (ng./ml.):			
Mean ± SD	14 ± 31.6	7 ± 6	0.003
Median	7.6	6.3	
Mean free/total PSA ± SD	14 ± 8	22 ± 10	0.0001
Mean IGF-1/PSA ± SD	27.8 ± 22	62.6 ± 13	0.0001
Mean IGF binding protein-3/PSA ± SD	444.7 ± 360	901 ± 204	0.001
Mean IGF binding protein-3/IGF-1 ± SD	16.8 ± 6	14.5 ± 3	0.0001

TABLE 3. *Prostate cancer in relation to quartiles of serum IGF-1 and IGF binding protein-3 before and after age adjustment*

Age Adjustment	Quartile 2 OR (95% CI)	Quartile 3 OR (95% CI)	Quartile 4 OR (95% CI)	p Value (test for trend)*
IGF-1:				
Before	0.8 (0.5–1.25)	0.8 (0.48–1.2)	0.9 (0.6–1.4)	0.15
After	0.3 (0.15–0.4)	0.2 (0.1–0.3)	0.4 (0.2–0.7)	0.001
IGF binding protein 3:				
Before	0.8 (0.5–1.4)	1.4 (0.9–2.2)	1 (0.6–1.5)	0.5
After	0.4 (0.2–0.7)	0.8 (0.5–1.4)	0.6 (0.36–1)	0.001

Quartile 1 reference value 1.
* Quartiles 2 to 4 versus 1.

TABLE 4. *Age adjusted IGF-1 and prostate volume according to total PSA*

PSA (ng./ml.)	Prostate Ca	Benign	p Value
Less than 4:			
No. pts.	41	69	
Mean vol. ± SD (gm.)	37 ± 15	44 ± 17	0.045
Mean IGF-1 ± SD (ng./ml.)	165.9 ± 48.1	198.5 ± 38.8	0.001
4–10:			
No. pts.	119	120	
Mean vol. ± SD (gm.)	52 ± 37	76 ± 40	0.0001
Mean IGF-1 ± SD (ng./ml.)	180.4 ± 59.1	191.0 ± 46.2	0.03
Greater than 10:			
No. pts.	71	42	
Mean vol. ± SD (gm.)	65 ± 24	86 ± 45	0.0001
Mean IGF-1 ± SD (ng./ml.)	174.1 ± 63.0	200.4 ± 48.0	0.03

TABLE 5. *Specificity of age adjusted PSA at different sensitivities*

	% Sensitivity		
	85	90	95
PSA	49	47	44
Free/total PSA	60	58	54
IGF-1	38	38	40
IGF binding protein-3	42	40	38
IGF-1/PSA	49	47	45
IGF binding protein-3/PSA	47	45	44
IGF binding protein-3/IGF-1	39	38	38

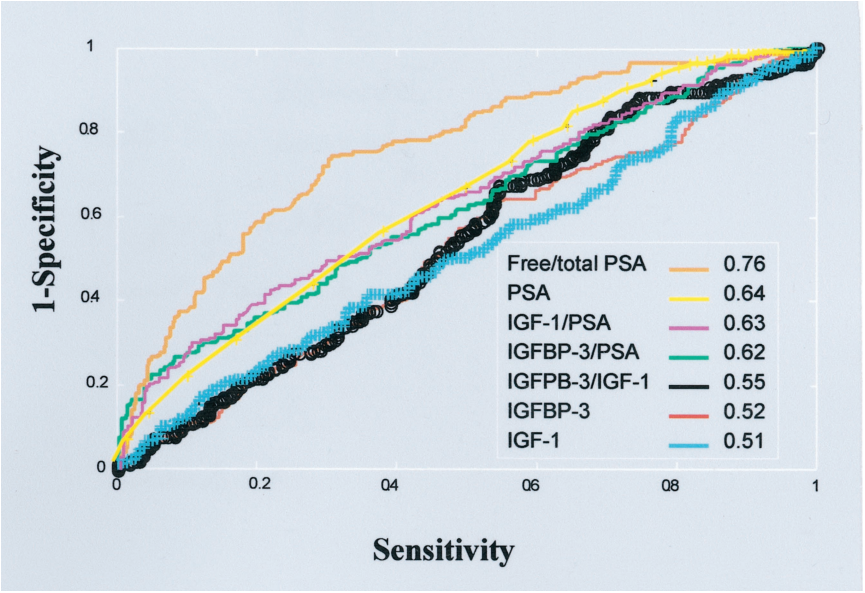
3-to-PSA ($p < 0.00001$) but no significance for IGF-1 or IGF binding protein-3 ($p = 0.43$ and 0.26, respectively).

DISCUSSION

The current study shows that in patients undergoing prostatic biopsy for elevated PSA or suspicious digital rectal examination there was no association of high serum IGF-1 or low serum IGF binding protein-3 with prostate cancer. In addition, after adjusting for age serum IGF-1 was significantly lower in these patients than in benign controls. This negative association of age adjusted IGF-1 and prostate cancer has been reported by others[16] but it contrasts with previous studies of IGF-1 and IGF binding protein-3 as markers of prostate cancer risk in unselected men.[3–10]

In contrast with earlier prospective studies of the hypothesis that IGF-1 and/or IGF binding protein-3 are related to the risk of prostate cancer,[3,6,7] our study was done in patients with elevated serum PSA or abnormal digital rectal examination suspicious for malignancy. Hence, these studies did not suggest that serum IGF-1 is a marker for prostate cancer detection, but rather that IGF-1 may be predictive of later cancer development. In addition, case-control studies that showed a correlation of higher serum IGF-1 with prostate cancer had control groups of select, age matched healthy individuals or patients with benign prostatic hyperplasia.[4,5,8–10] Our control group underwent transrectal ultrasound guided prostate biopsy due to elevated serum PSA or abnormal digital rectal examination. Furthermore, in the initial case-control studies of Mantzoros[4] and Wolk[5] et al PSA in their cohort was not reported, which may further explain the difference in studies. Interestingly a recent report of these groups mentioned no correlation of serum IGF-1 with prostate cancer in patients with PSA greater than 3 μg./l.[19]

According to our data the IGF-1-to-PSA and IGF binding protein-3-to-PSA ratios were significantly lower in men with cancer than in benign controls. This finding was likely due to the fact that PSA was significantly higher in the cancer



ROC curves for sensitivity versus 1 − specificity for IGF-1, IGF binding protein-3, IGF binding protein-3 (*IGFBP-3*)-to-IGF-1, IGF binding protein-3-to-PSA, IGF-1-to-PSA, PSA and free-to-total PSA.

group. Moreover, the AUC for IGF-1-to-PSA and IGF binding protein-3-to-PSA was lower than that for serum PSA (0.63 and 0.62 versus 0.64, respectively), indicating that these ratios do not improve the accuracy of PSA alone for distinguishing cancer. Djavan et al reported that a higher IGF-1-to-PSA ratio significantly improved prostate cancer detection compared with PSA alone in 71 patients with cancer with PSA between 2.5 and 15 μg./l.[12] Our data do not support their observation since in our patient cohort the IGF-1-to-PSA ratio was significantly lower in the cancer than in the benign control group. This discrepancy may be explained by the small number of patients with prostate cancer patients in their study (71 versus 174). In addition, our patients had a wider range of PSA (mean 9.75 ± 20.2 μg./l., 95% CI 8.2 to 11.3). Nevertheless, when examining patients with PSA less than 10 μg./l., IGF-1-to-PSA and IGF binding protein-3-to-PSA were not statistically significant ($p = 0.5$ and 0.4, respectively).

When classifying according to serum PSA, (table 4) a negative association was observed because serum IGF-1 was significantly higher in benign controls than in men with cancer ($p = 0.001$ and 0.03, respectively, table 4). Benign controls had high PSA, which in the absence of cancer can be explained by a large prostate volume. Hence, this association of high IGF-1 with benign controls may be explained by a larger prostate volume in different PSA categories, as previously reported.[16] A strong association of high IGF-1 with an enlarged prostate was observed in men with acromegaly who had elevated serum growth hormone and IGF-1, while small prostates were noted in growth hormone deficient adults.[20] Our results suggest that the relationship of IGF-1 to prostate volume is present in all men rather than confined to those with pathologically high or low IGF-1.

Notably other studies with a different design failed to show any significant correlation of IGF-1 or IGF binding protein-3 with prostate cancer.[11–14] To our knowledge only 2 studies had a design similar to ours,[15,16] and they showed a lack of correlation of IGF-1 with prostate cancer detection in patients undergoing prostate biopsy, including 1 done in 665 patients with elevated PSA[16] and 1 done in 94 patients.[15] The current study was performed in a large cohort of patients in which we determined that IGF-1, IGF binding protein-3, IGF binding protein-3-to-IGF-1, IGF-1-to-PSA and IGF binding protein-3-to-PSA are not useful markers for prostate cancer detection in patients undergoing prostate biopsy. It is important to emphasize that the design of the current and previous similar studies[15,16] related to IGF-1 as a diagnostic marker for prostate cancer, which is distinct from the separate issue of IGF-1 as a risk factor for this disease. In conclusion, in men with elevated serum PSA or abnormal digital rectal examination who undergo prostatic biopsy measuring serum IGF-1 and/or IGF binding protein-3 does not improve the accuracy of PSA or free-to-total PSA for diagnosing prostate cancer.

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