

Serum insulin-like growth factor (IGF)-1 and IGF-binding protein-3 do not correlate with Gleason score or quantity of prostate cancer in biopsy samples

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OBJECTIVE

To examine the relationship of serum insulin-like growth factor (IGF)-1 and IGF binding protein-3 (IGFBP-3) with histological cancer characteristics in men undergoing transrectal ultrasonography (TRUS)-guided biopsy.

PATIENTS AND METHODS

Patients (652), with either an elevated serum prostate-specific antigen level or an abnormal digital rectal examination, were initially evaluated by TRUS and sextant prostatic needle biopsy. Blood was drawn before biopsy, serum extracted and stored frozen until IGF-1 and IGFBP-3 were measured. In all, 241 patients had prostate cancer (37%) and were included in this study. The number of positive

biopsies, the volume of tumour in each positive biopsy and the Gleason score were recorded.

RESULTS

Of the 241 patients, 37 had five or six positive biopsies (from six), 128 had two to four and 76 had one. Serum IGF-1 did not correlate with the number of positive biopsies, with means of 176.7, 178.3 and 164.4 ng/mL, respectively ($P=0.3$), while the mean IGFBP-3 was 2695, 2795 and 2572 ng/mL, respectively ($P=0.09$). The additive percentiles of tumour volume in positive biopsies were assessed for each patient but serum IGF-1 and IGFBP-3 did not correlate ($P=0.7$ and 0.9 , respectively). In all, 92 patients had a Gleason score of <7 , 80 a score of 7 and 69 a score of >7 ; the

mean (sd) IGF-1 levels for the three groups were 181 (39), 174.6 (35) and 176 (26) ng/mL, and the mean IGFBP-3 2798 (240), 2735 (284) and 2647 (221) ng/mL, respectively, none of the differences being statistically significant.

CONCLUSIONS

Serum IGF-1 and IGFBP-3 do not correlate with quantity of cancer or Gleason score in biopsy samples from patients with prostate cancer.

KEYWORDS

insulin-like growth factor, IGF-1, IGFBP3, prostate cancer, prediction

INTRODUCTION

The IGFs are potent mitogens and anti-apoptotic molecules involved in regulating cell proliferation and differentiation in different organs, including the prostate [1]. Several epidemiological studies reported that an increased risk of prostate cancer is associated with high serum IGF-1, while a high serum IGF binding protein (BP)-3 level was associated with a reduced risk [4–8]. These results suggest that high serum levels of IGF-1, and low serum levels of IGFBP-3, are risk factors for the future development of prostate cancer. However, studies examining the relationship of serum IGF and IGFBP-3 in prostate cancer detection have yielded conflicting results [9–16].

The intraprostatic expression of IGF-1 and IGFBP-3 are associated with tumour grade, pathological stage and disease progression [17–19]. However, the value of serum IGF-1

and/or IGFBP-3 as markers for locally advanced or metastatic prostate cancer, or as predictors of recurrence, is unclear. Several studies [7,14,20,21] found no association between serum IGF-1, IGFBP-3 and tumour grade or pathological stage in patients with clinically localized prostate cancer undergoing radical prostatectomy, while others found no predictive value for IGF-1 and IGFBP-3 in the prognosis of prostate cancer [21,22]. Conversely, a low serum IGFBP-3 level was shown to be associated with metastatic prostate cancer [23,24], and a more recent report suggested it to be an independent predictor of biochemical progression after surgery for localized prostatic disease [24].

Serum IGF-1 and/or IGFBP-3 were reportedly not useful as serum tests for detecting prostate cancer, as they do not improve the accuracy of PSA or free/total PSA in patients undergoing TRUS-guided biopsy [15,16]. The

aim of the present study was to assess the correlation of serum IGF-1 and IGFBP-3 levels with adverse pathological features, e.g. grade and quantity of cancer, in patients with prostate cancer confirmed by biopsy.

PATIENTS AND METHODS

The study initially included 652 consecutive patients with a high serum PSA level or a suspicious DRE who were evaluated at a prostate cancer detection clinic between January 1998 and October 1999 [16,24]. After obtaining informed consent, blood samples were drawn before any prostatic manipulation, followed by TRUS-guided prostate biopsy with at least six biopsies taken [16]; all biopsies were examined by one uropathologist (L.R.B.).

Of these patients, 244 (37.4%) were diagnosed with prostate cancer and 241 had

adequate biopsy material to be included in the present study. The extent of cancer was assessed by the number of positive biopsies (for each patient), the volume of tumour (measured as a percentage of cancer per core) and the Gleason grade. Furthermore, the additive volumes of tumour in all positive biopsies were recorded as another indicator of the tumour burden. Prostate volume was estimated by TRUS as: $\pi/6 \times$ (transverse \times anteroposterior \times cephalo-caudal) diameters.

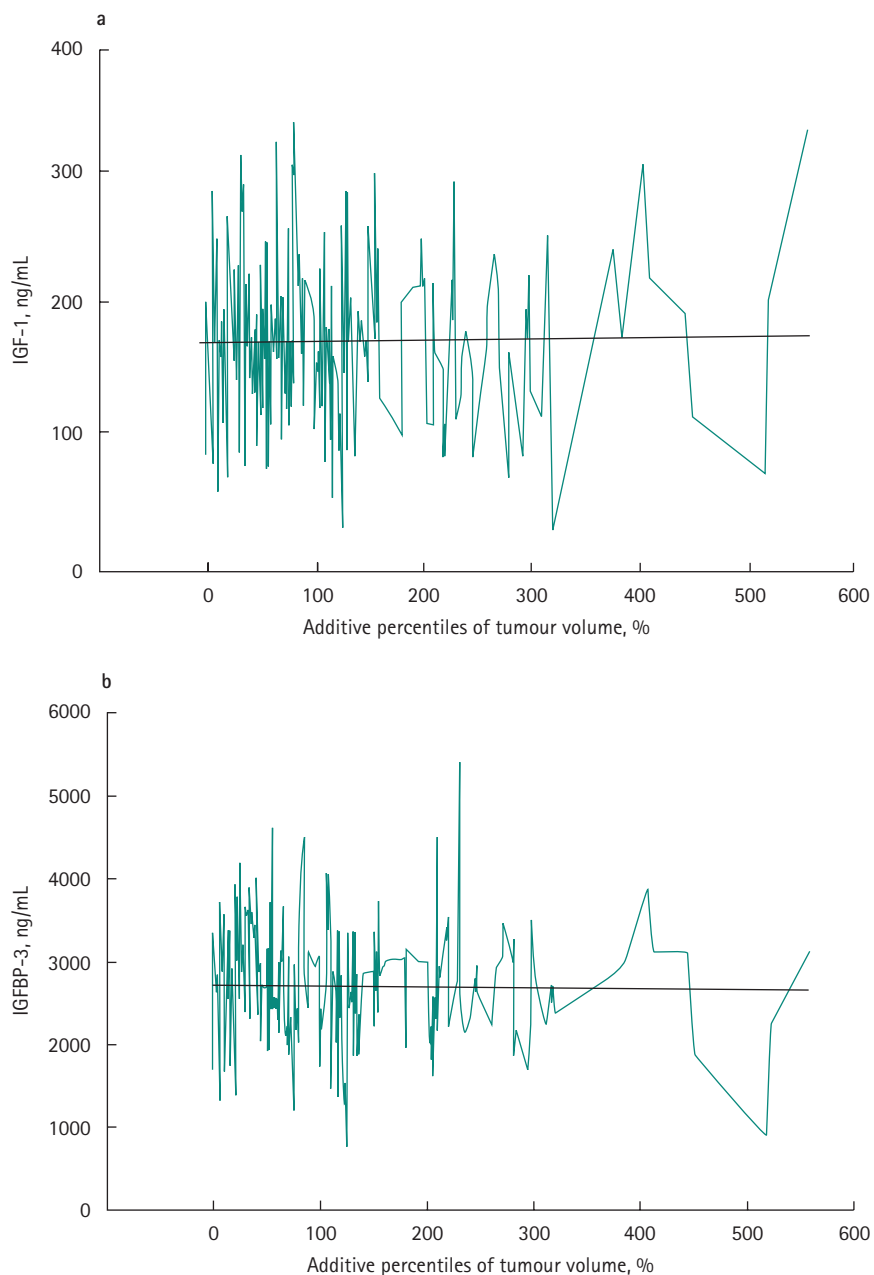
Before biopsy, all patients had a blood sample taken for the analysis of PSA, free/total PSA, IGF-1 and IGFBP-3. After centrifugation the serum obtained was stored at -80°C until analysis. IGF-1 and IGFBP-3 were analysed by an ELISA (Diagnostic Systems Laboratory, Webster, Texas, USA), as described previously [4,16]. Serum IGF-1, IGFBP-3-values were assessed statistically both unmatched and age-matched, with the ages matched individually using a random process of age-matched subject selection according to age \pm 1 year [5].

RESULTS

For all 241 men the mean (SD) age was 65.2 (6.7) years, and the mean IGF-1 and IGFBP-3 levels 176.1 (58.3) and 2724 (647) ng/mL, respectively. The mean (SD, range, median) PSA level was 13.9 (31, 1–424, 7.7) ng/mL. Forty-one patients (17%) had PSA levels of <4 ng/mL, 129 (54%) of 4–10 ng/mL and 71 (29%) of ≥ 10 ng/mL. The mean (SD) serum IGF-1 levels in these different PSA groups were 165.9 (48.1), 180.4 (59.1) and 174.1 (63) ng/mL, respectively ($P=0.4$), and the IGFBP-3 levels 2657 (531), 2791 (645) and 2643 (600) ng/mL, respectively ($P=0.5$). Serum IGF-1 and IGFBP-3 levels decreased significantly with increasing age among the patients ($P < 0.001$ and 0.007 , respectively), and therefore further analysis included an age adjustment.

Age-adjusted serum IGF-1 and IGFBP-3 showed no correlation with tumour grade (Table 1, $P=0.8$ and 0.5 , respectively). Table 1 also shows the age-adjusted IGF-1 and IGFBP-3 levels in patients with different numbers of positive sextant biopsies, where 76 (31.5%) had one positive biopsy and mean IGF-1 and IGFBP-3 levels of 164.4 and 2572 ng/mL, 128 (53%) had two to four positive biopsies with mean IGF-1 and IGFBP-3 levels of 178.3 and 2795 ng/mL, and 37 had

FIG. 1. Age-adjusted **a**, serum IGF-1 and **b**, IGFBP-3 levels, and the additive tumour volumes in positive sextant biopsies for each patient. The green line shows the observed values and the black line the fitted regression.



five or six positive biopsies, with mean IGF-1 and IGFBP-3 levels of 176.7 and 2695 ng/mL ($P=0.3$ and 0.09 , respectively). The additive percentiles of tumour volume in positive biopsies were assessed for each patient (range 5–550%). Serum IGF-1 and IGFBP-3 levels showed no association with this adverse pathological variable ($P=0.7$ and 0.9 , respectively; Fig 1a,b). There was a significant

positive correlation between age-adjusted IGF-1 level and prostate volume ($P < 0.001$), but no correlation between serum IGFBP-3 and prostate volume ($P=0.5$).

DISCUSSION

The present study shows that for patients with prostate cancer undergoing TRUS for a

Variable [n]	Mean (Sd)	
	IGF-1, ng/mL	IGFBP-3, ng/mL
Gleason score		
< 7 [92]	181 (39)	2798 (240)
7 [80]	174.6 (35)	2735 (284)
> 7 [69]	176 (26)	2647 (221)
Number of positive biopsies		
1/6 [76]	164.4 (31)	2572 (580)
2/6 [54]	178.9 (66)	2785 (733)
3/6 [47]	187.2 (52)	2868 (577)
4/6 [27]	168.8 (49)	2732 (558)
5/6 [19]	159.8 (57)	2456 (386)
6/6 [18]	193.6 (78)	2933 (908)

TABLE 1
The age-adjusted IGF-1 and IGFBP-3 levels in different groups of Gleason score and the number of positive TRUS-guided prostate biopsies

high PSA level or a suspicious DRE, there was no association between age-adjusted serum IGF-1 and IGFBP-3 levels, and histological grade or quantity of cancer. Serum IGF-1 and IGFBP-3 levels did not correlate with tumour grade, the number of positive prostatic biopsies, or the additive tumour volumes in positive biopsies. We acknowledge that pathological features obtained from sextant biopsies do not always correlate with those of radical prostatectomy specimens. It is possible that with more biopsies per patient there would be a different outcome. However, these data agree with those from previous studies [7,14,20,21] which found no correlation between serum IGF-1, IGFBP-3 and clinical stage or pathological grade in patients with localized prostate cancer undergoing radical prostatectomy. Nevertheless, low serum IGFBP-3 has been reported to be associated with metastatic prostate cancer [23], and to be a preoperative predictor of biochemical progression after prostatectomy [23]. In that study the authors reported no correlation between serum IGFBP-3 level and adverse pathological features.

Local tissue expression could conceivably be more important than circulating levels of growth factors. IGF-1 and IGFBP-3 mRNA and/or proteins have been identified in malignant prostatic tissues [17–19,25,26], where decreased local expression of IGFBP-3 has been associated with higher grade tumours [17–19]. For IGF-1, despite there being no increased local expression in locally aggressive prostate tumours [25,26], this was explained because prostatic tissues are more sensitive to IGF-1 stimulation, as there is a 10-fold up-regulation in IGF-1R expression [28]. Hence, normal circulating IGF-1 levels may have a greater effect on malignant than on normal prostatic tissues.

In conclusion, from recent studies on patients with elevated PSA levels or an abnormal DRE undergoing TRUS-guided biopsy, the serum IGF-1 and IGFBP-3 levels do not improve prostate cancer detection, nor do they correlate with the grade or quantity of cancer.

REFERENCES

- 1 Pollak M. Insulin-like growth factor and prostate cancer. *Am J Epidemiol* 2001; **23**: 59–66
- 2 Rajaram S, Baylink DJ, Mohans S. Insulin-like growth factor-binding proteins in serum and other biological fluids: regulation and functions. *Endocrinol Rev* 1997; **18**: 801–31
- 3 Martin JL, Baxter RC. Insulin-like growth factor binding protein-3: biochemistry and physiology. *Growth Regul* 1992; **2**: 88–99
- 4 Chan JM, Stampfer MJ, Gionannucci E *et al*. Plasma insulin-like growth factor-1 and prostate cancer risk: a prospective study. *Science* 1998; **279**: 563–6
- 5 Mantzoros CS, Tzonou A, Signorello LB, Stampfer M, Trichopoulos D, Adami H-O. Insulin-like growth factor-1 in relation to prostate cancer and benign prostatic hyperplasia. *Br J Cancer* 1997; **76**: 1115–8
- 6 Wolk A, Mantzoros CS, Andersson S-O *et al*. Insulin-like growth factor-1 and prostate cancer risk: a population-based case-control study. *J Natl Cancer Inst* 1998; **90**: 911–5
- 7 Stattin P, Bylund A, Rinaldi S *et al*. Plasma insulin-like growth factor-1, insulin-like growth factor-binding proteins, and prostate cancer risk: a prospective study. *J Natl Cancer Inst* 2000; **92**: 1910–7
- 8 Harman SM, Metter EJ, Blackman MR, Landis PK, Carter HB. Serum levels of

insulin-like growth factor I (IGF-I), IGF-II, IGF-binding protein-3, and prostate specific antigen as predictors of clinical prostate cancer. *J Clin Endocrinol Metab* 2000; **85**: 4258–65

- 9 Kanety H, Madjar Y, Dagan Y *et al*. Serum insulin-like growth factor-binding protein-2 (IGFBP-2) is increased and IGFBP-3 is decreased in patients with prostate cancer: correlation with serum prostate-specific antigen. *J Clin Endocrinol Metab* 1993; **77**: 229–33
- 10 Chokkalingam AP, Pollak M, Fillmore CM *et al*. Insulin-like growth factor and prostate cancer: a population-based case-control study in China. *Cancer Epidemiol Biomarkers Prev* 2001; **10**: 421–7
- 11 Khosravi J, Diamandi A, Mistry J, Scorilas A. Insulin-like growth factor I (IGF-I) and IGF-binding protein-3 in benign prostatic hyperplasia and prostate cancer. *J Clin Endocrinol Metab* 2001; **86**: 694–9
- 12 Schäfer C, Friedman GD, Quesenberry CP Jr. IGF-1 and prostate cancer. *Science* 1998; **282**: 199–204
- 13 Kurek R, Tunn UW, Eckart O, Aumuller G, Wong J, Renneberg H. The significance of serum levels of insulin-like growth factor-1 in patients with prostate cancer. *BJU Int* 2000; **85**: 125–9
- 14 Ho PJ, Baxter RC. Insulin-like growth factor-binding protein-2 in patients with prostate carcinoma and benign prostatic hyperplasia. *Clin Endocrinol* 1997; **46**: 333–42
- 15 Cutting CW, Hunt C, Nisbet JA, Bland JM, Dalglish AG, Kirby RS. Serum insulin-like growth factor-1 is not a useful marker of prostate cancer. *BJU Int* 1999; **83**: 996–9
- 16 Ismail HA, Pollak M, Behlouli H, Tanguay S, Bégin LR, Aprikian AG. Insulin-like growth factor-1 and IGF-binding protein-3 for prostate cancer detection in patients undergoing prostate biopsy. *J Urol* 2002; **168**: 246–30
- 17 Tennant MK, Thrasher JB, Twomey PA, Birnbaum RS, Plymate SR. Insulin-like growth factor-binding protein-2 and -3 expression in benign human prostate epithelium, prostate intraepithelial neoplasia, and adenocarcinoma of the prostate. *J Clin Endocrinol Metab* 1996; **81**: 411–20
- 18 Thrasher JB, Tennant MK, Twomey PA, Hansberry KL, Wettlaufer JN, Plymate SR. Immunohistochemical localization of insulin-like growth factor-binding

protein-2 and -3 in prostate tissue: clinical correlation. *J Urol* 1996; **155**: 999–1003

- 19 **Figuroa JA, De Raad S, Tadlock L, Speights VO, Rinehart JJ.** Differential expression of insulin-like growth factor-binding proteins in high versus low Gleason score prostate cancer. *J Urol* 1998; **159**: 1379–83
- 20 **Latif Z, McMillan DC, Wallace AM et al.** The relationship of circulating insulin-like growth factor-1, its binding protein-3, prostate-specific antigen and C-reactive protein with disease stage in prostate cancer. *BJU Int* 2002; **89**: 396–9
- 21 **Shariat SF, Bergamaschi F, Adler HL et al.** Correlation of preoperative plasma IGF-1 levels with pathological parameters and progression in patients undergoing radical prostatectomy. *Urology* 2000; **56**: 423–9
- 22 **Yu H, Nicar MR, Shi R et al.** Levels of insulin-like growth factor I (IGF-I) and IGF binding proteins 2 and 3 in serial postoperative serum samples and risk of prostate cancer recurrence. *Urology* 2001; **57**: 471–5
- 23 **Shariat SF, Lamb DJ, Kattan MW et al.** Association of preoperative plasma levels of insulin-like growth factor I and insulin-like growth factor-binding protein-2 and -3 with prostate cancer invasion, progression, and metastasis. *J Clin Oncol* 2002; **20**: 833–41
- 24 **Karakiewicz PI, Bazinet M, Aprikian AG et al.** Outcome of sextant biopsy according to gland volume. *Urology* 1997; **49**: 55–9
- 25 **Figuroa JA, De Raad S, Speights VO, Rinehart JJ.** Gene expression of insulin-like growth factors and receptors in neoplastic prostate tissues: correlation with clinico-pathological parameters. *Cancer Invest* 2001; **19**: 28–34
- 26 **Mita K, Nakahara M, Usui T.** Expression of the insulin-like growth factor system and cancer progression in hormone-treated prostate cancer patients. *Int J Urol* 2000; **7**: 321–9
- 27 **Kurek R, Tunn UW, Aumüller G et al.** Insulin-like growth factor 1 (IGF-1) and insulin-like growth-factor receptor 1 (IGFR-1) in prostate cancer. *J Urol* 2000; **163**: A35

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Abbreviations: –1R, type 1 receptor; BP, binding protein.