

Comparison of Chromogranin A, Insulin-Like Growth Factor 1 and Prostate-Specific Antigen Serum Markers in Prostate Adenocarcinoma and Benign Prostatic Hyperplasia

Alessandro Sciarra^a Vincenzo Gentile^a Salvatori Monti^b Cristian Dattilo^a
Anna Autran Gomez^a Stefano Salciccia^a Laura Proietti Pannunzi^b
Vincenzo Toscano^c Franco Di Silverio^a

Departments of ^aUrology and ^bEndocrinology, University of Rome, and ^cDepartment of Endocrinology, Sant'Andrea Hospital, University of Rome, Rome, Italy

Key Words

Prostate neoplasm · Serum marker · Prostate-specific antigen · Chromogranin A · Insulin-like growth factor

Abstract

Background/Aim: To compare serum chromogranin A (CgA) and insulin-like growth factor 1 (IGF-1) with the classical prostate-specific antigen (PSA) marker in clinically localized prostate adenocarcinomas. **Materials and Methods:** This is a prospective single-center study that included 64 consecutive men with newly diagnosed clinically localized prostate adenocarcinoma and 20 consecutive men with histologically confirmed benign prostatic hyperplasia (BPH). A blood sample for the determination of serum total PSA, CgA and IGF-1 levels (RIA) was obtained from all cases. Analysis of variance was performed to evaluate their variations according to disease and the pathological characteristics of prostate adenocarcinoma. **Results:** Only serum PSA levels ($p < 0.0001$) and not IGF-1 ($p = 0.5475$) or CgA ($p = 0.5043$) were significantly higher in the prostate cancer (PCa) group as compared to the BPH group. A significant variance between

BPH and PCa divided on the basis of pT stage was found for PSA levels ($p < 0.0001$) but not for CgA ($p = 0.0869$) and IGF-1 ($p = 0.6883$) levels. Dividing PCa on the basis of Gleason score, a significant variance was found for CgA ($p = 0.0100$) and for PSA ($p < 0.001$), but not for IGF-1 ($p = 0.6895$) levels. **Conclusions:** In our population the quantification of PSA and CgA serum levels and not of IGF-1 provides independent significant information in the diagnosis and aggressiveness of PCa, respectively.

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Introduction

In patients with newly diagnosed prostate cancer (PCa), the better-defined prognostic predictors are staging, Gleason score and serum prostate-specific antigen (PSA) levels at diagnosis [1]. It is still important to establish and to compare the role of different serum predictors and markers in prostate adenocarcinoma. Prostatic neuroendocrine cells play an important role in the growth and differentiation of the prostate gland. Prostate adeno-

Table 1. Clinical and pathological characteristics of BPH and PCa patients

	PCa patients	BPH patients	p (Mann-Whitney test)
Cases	64	20	–
Age, years	67.24 ± 5.19 (68); 50–75	67.06 ± 7.09 (68); 55–78	0.7785
PSA, ng/ml	14.59 ± 6.76 (13.25); 4.20–32.0	1.48 ± 1.11 (1.01); 0.50–3.90	<0.0001
CgA, ng/ml	57.09 ± 27.97 (55.55); 21.13–146.0	56.46 ± 20.44 (57.55); 18.10–98.0	0.5043
IGF-1, ng/ml	150.87 ± 106.48 (110.84); 22.38–572.86	132.57 ± 85.63 (143.25); 9.0–323.0	0.5475
pT2	36	–	–
pT3	28	–	–
Gleason ≤7(3+4)	37	–	–
Gleason ≥7(4+3)	27	–	–

Values are expressed in number of cases or in mean ± SD (median) and range. The Mann-Whitney test was used to evaluate p values between the BPH and PCa groups.

carcinomas displaying neuroendocrine differentiation tend to be more aggressive [2, 3]. With regard to PCa, chromogranin A (CgA) is the most employed serum marker to detect neuroendocrine features [4] and different publications have provided evidence for a diagnostic and prognostic significance of CgA circulating levels [4–7]. Insulin-like growth factor 1 (IGF-1) is a growth hormone-dependent peptide related to cell growth and differentiation [8–10]. The interest in IGF-1 for prostate adenocarcinoma was primarily triggered by prospective studies providing evidence for a relationship between IGF-1 serum levels and the risk of PCa development and progression [11, 12].

The aim of the present study was to compare serum CgA and IGF-1 with the classical PSA marker value in patients with clinically localized prostate adenocarcinoma.

Materials and Methods

Patients

This prospective single-center study that took place between January 2004 and January 2005, included 64 consecutive men with newly diagnosed clinically localized prostate adenocarcinoma and 20 consecutive men with newly diagnosed lower urinary tract symptoms secondary to histologically confirmed benign prostatic hyperplasia (BPH). All PCa cases were submitted to radical prostatectomy (RRP) and all BPH cases were submitted to transurethral resection of the prostate. Inclusion into the study was based on the following criteria: (a) patients with clinically localized PCa and patients with lower urinary tract symptom secondary to BPH; (b) no previous hormonal or radiation or chemotherapy; (c) no previous surgery on prostate gland, and (d) histologically proven adenocarcinoma of the prostate at RRP and histologically proven BPH at surgery.

None of the 64 PCa cases and none of the 20 BPH cases presented a history of other disorders or therapies or conditions known to interfere with CgA and IGF-1 serum levels.

In the PCa group, initial diagnosis was obtained by transrectal ultrasound-guided biopsies and a clinically localized stage was determined by digital rectal examination, transrectal ultrasonography and bone scan in all cases. In all patients the diagnosis of prostate adenocarcinoma was histologically confirmed at RRP. On the basis of the histological grade obtained at RRP, PCa patients were divided into two groups: Gleason score ≤7(3+4) and Gleason score ≥7(4+3). On the basis of the pathological stage, PCa cases were divided into localized (pT2) and locally advanced (pT3). No pT4 and only 3 N+ cases (all pT3) were found in this experiment. In the BPH group, mean IPSS score was 13.85 ± 3.04 (median 14; range 9–20) and mean prostate volume (ellipsoid method at transrectal ultrasonography) was 42.55 ± 7.15 ml (median 40.0; range 33.0–66.0 ml). In all cases the diagnosis of BPH was histologically confirmed after surgery. Clinical and pathological characteristics of the prostate adenocarcinoma and BPH cases are described in table 1.

Methods

On the same day as RRP or BPH surgery, before the surgical procedure but at least 3 weeks after any prostatic manipulation, a blood sample for the determination of preoperative serum total PSA, CgA and IGF-1 levels was obtained from all patients. Serum total PSA was measured by RIA (Hybritech, Inc., San Diego, Calif., USA) in each case. The detection limit of this kit was 0.04 ng/ml. The inter- and intra-assay coefficients of variations of PSA assay were 3.95 and 1.85%, respectively. The same serum sample was used to determine CgA levels by RIA using a commercial kit (CIS bio International, Bagnols-sur-Cèze, France). The detection limit of this kit was 1.5 ng/ml. The inter- and intra-assay coefficients of variations of CgA assay were 6.5 and 4%, respectively. In all cases the same serum sample was also used to determine IGF-1 levels using the DSL-500 assay (Diagnostic System Laboratories, Inc., Webster Tex., USA). The detection limit of this kit was 0.8 ng/ml. The inter- and intra-assay coefficients of variations of IGF-1 assay were 4.4 and 2.6%, respectively.

Statistical Analysis

All statistical analyses were conducted using SigmaStat and SigmaPlot 9.0 programs. Spearman correlation coefficients were calculated to measure the association among serum markers CgA, IGF-1 and PSA and the other parameters (age, pathological T stage and Gleason score). Variations in the serum markers PSA, CgA and IGF-1 in each group were reported using the Mann-Whitney test. A one-way analysis of variance (ANOVA) model was also used. PSA, CgA and IGF-1 were always used as continuous variables. All statistical tests were two-sided and statistical significance was set at $p < 0.05$.

Results

A total of 84 men entered this study: 64 (67.24 ± 5.19 years; median 68) with newly diagnosed histologically confirmed prostate adenocarcinoma and 20 (67.06 ± 7.09 years; median 68) with histologically confirmed BPH.

Serum Markers PSA, IGF-1 and CgA:

Comparison between PCa and BPH Cases

Serum PSA levels were significantly higher in the PCa group as compared to the BPH group ($p < 0.0001$) (table 1; fig. 1a). Serum IGF-1 levels did not significantly differ between the PCa group and BPH group ($p = 0.5475$) (table 1; fig. 1b). CgA serum levels were also not significantly different between the PCa group and BPH group ($p = 0.5043$) (table 1; fig. 1c). Analyzing the associations (Spearman coefficient r) among the three serum markers PSA, IGF-1 and CgA either in the BPH or PCa group, no significant values were found (PCa group: CgA-PSA: $r = 0.0008$, $p = 0.9947$; CgA-IGF-1: $r = -0.1484$, $p = 0.2420$; IGF-1-PSA: $r = -0.1238$, $p = 0.3297$; BPH group: CgA-PSA: $r = -0.2439$, $p = 0.4918$; CgA-IGF-1: $r = -0.2826$, $p = 0.2411$; IGF-1-PSA: $r = 0.3597$, $p = 0.0962$).

The impact of age on PSA, IGF-1 and CgA levels was also analyzed separately for PCa and BPH patients. Either in the BPH or PCa group, there were no significant associations ($p > 0.05$) between patient age and PSA (BPH: $r = 0.1098$, $p = 0.7589$; PCa: $r = 0.0927$, $p = 0.3820$) or between age and IGF-1 (BPH: $r = -0.2051$, $p = 0.1040$; PCa: $r = -0.0616$, $p = 0.1232$) levels. On the contrary, a significant positive association between CgA and age was found only in BPH cases (BPH: $r = 0.3126$, $p = 0.0089$; PCa: $r = 0.2656$, $p = 0.0619$).

Serum Markers PSA, IGF-1 and CgA: Influence of Pathological Tumor Stage

In the PCa group, serum PSA and IGF-1 levels were comparable between pT2 and pT3 cases (PSA: pT2 =

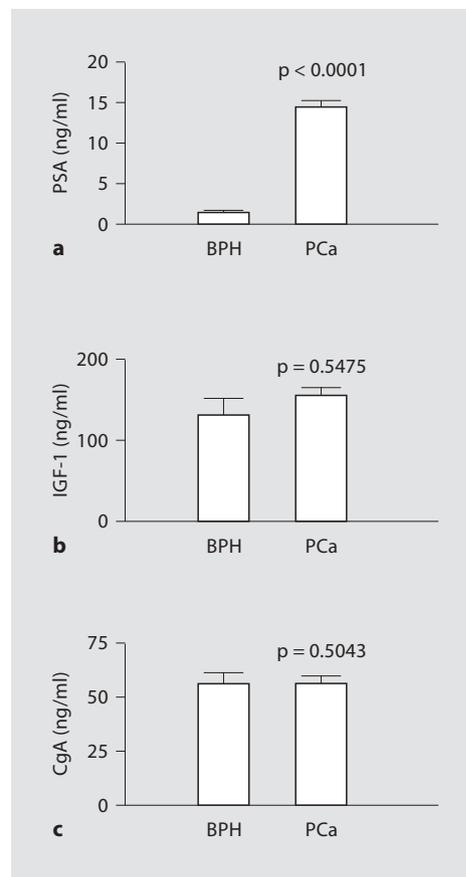


Fig. 1. Mean \pm SD of serum marker PSA (a), IGF-1 (b) and CgA (c) levels: comparison between BPH and prostate adenocarcinoma (PCa) group. The Mann-Whitney test was used to evaluate p values.

14.07 ± 6.55 (12.20) 4.20–32.0; pT3 = 15.72 ± 7.04 (17.0) 4.20–26.0, $p = 0.2626$; IGF-1: pT2 = 150.69 ± 91.91 (126.91); 22.38–358.01; pT3 = 158.52 ± 121.71 (103.15); 45.69–572.86, $p = 0.7556$). Serum CgA levels were higher in pT3 when compared to pT2 cases but the difference did not reach statistical significance (pT2: 51.72 ± 20.14 (48.35) 22.50–115.30; pT3: 67.90 ± 36.12 (58.85) 21.13–146.0, $p = 0.1540$). A significant variance between BPH and PCa, divided on the basis of pT stage, was found for PSA levels ($p < 0.0001$) but not for CgA ($p = 0.0869$) and IGF-1 ($p = 0.6883$) levels (fig. 2). In particular, for PSA a statistically significant difference was found either between BPH and pT2 ($p < 0.0001$) or BPH and pT3 ($p < 0.0001$) tumors. Considering CgA levels, a statistically significant difference was found only between BPH and pT3 ($p = 0.0454$) and not between BPH and pT2 ($p = 0.5468$) tumors.

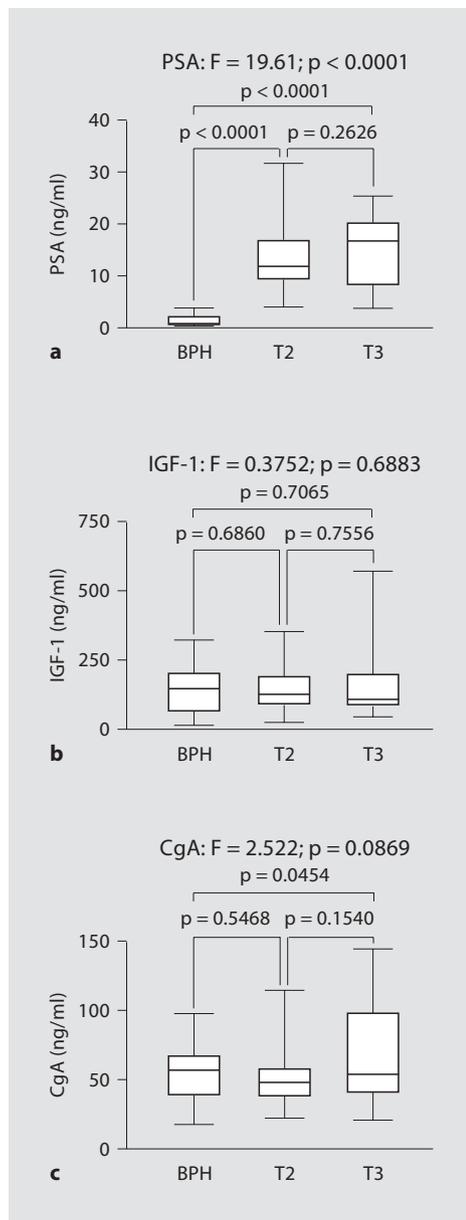


Fig. 2. One-way ANOVA model: variance in serum marker PSA (a), IGF-1 (b) and CgA (c), according to the diagnosis of BPH and prostate adenocarcinoma divided on the basis of pathological stage (pT2 and pT3).

Serum Markers PSA, IGF-1 and CgA: Influence of RRP Tumor Grading

In the PCa group, serum PSA and IGF-1 levels were comparable between Gleason score $\leq 7(3+4)$ and Gleason score $\geq 7(4+3)$ cases (PSA: pT2 = 13.73 ± 6.93 (12.0) 4.20–28.0; pT3 = 16.32 ± 6.33 (16.0) 6.40–32.0, $p = 0.1068$; IGF-1: pT2 = 157.38 ± 91.72 (142.0); 22.38–420.07; pT3 = 149.65 ± 122.97 (98.0); 55.75–572.86, $p = 0.211$). On the

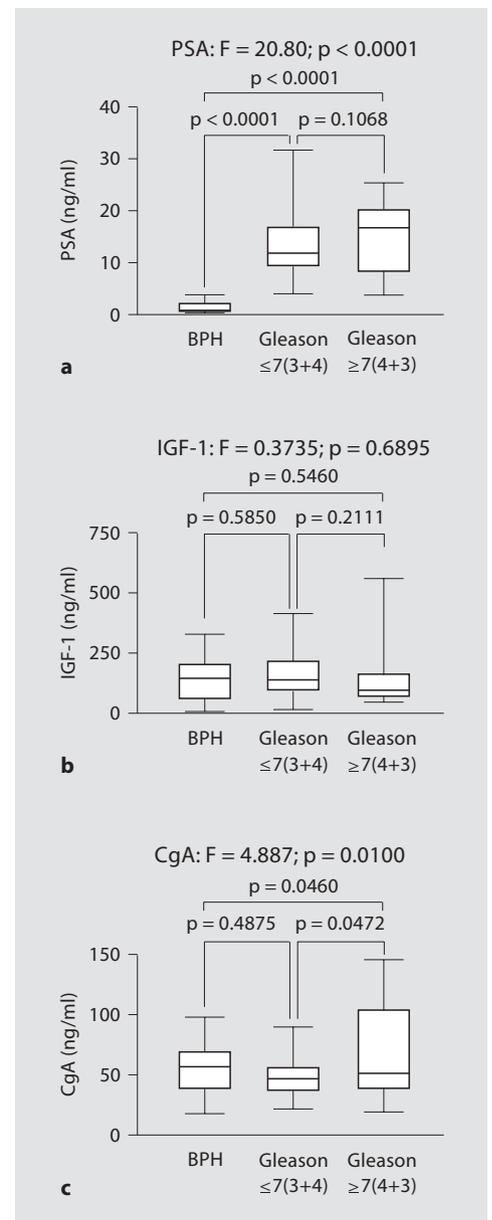


Fig. 3. One-way ANOVA model: variance in serum marker PSA (a), IGF-1 (b) and CgA (c), according to the diagnosis of BPH and prostate adenocarcinoma divided on the basis of Gleason score ($\leq 7(3+4)$ and $\geq 7(4+3)$).

contrary, serum CgA levels were significantly higher in Gleason score $\geq 7(4+3)$ when compared to Gleason score $\leq 7(3+4)$ cases (pT2 = 48.12 ± 16.42 (47.80) 22.22–90.91; pT3 = 68.53 ± 36.05 (52.90) 21.13–146.0, $p = 0.0472$).

A statistically significant variance between BPH and PCa cases, divided on the basis of the Gleason score, was found for CgA ($p = 0.0100$) and for PSA ($p < 0.0001$) but not for IGF-1 ($p = 0.6895$) levels (fig. 3). In particular, for

PSA a statistically significant difference was found either between BPH and Gleason score $\leq 7(3+4)$ ($p < 0.0001$) or BPH and Gleason score $\geq 7(4+3)$ ($p < 0.0001$) tumors. Considering CgA levels, a statistically significant difference was found only between BPH and Gleason score $\geq 7(4+3)$ ($p = 0.0460$) but not between BPH and Gleason score $\leq 7(3+4)$ ($p = 0.4875$) tumors.

Discussion

This study gives the opportunity to analyze and to compare in the same homogeneous population three different possible serum markers in PCa. In particular, the purpose was to analyze and to compare the serum level of PSA, CgA and IGF-1 as markers of PCa, according to the aggressiveness of the tumor, either in terms of pathological stage or of Gleason score. For this reason, as in previous studies [1, 13], we prospectively selected a population of newly diagnosed clinically localized prostate adenocarcinomas. To assess the concentration and variations in these three serum peptides according not only to the diagnosis of PCa but also to the pathological T stage and grading of the tumor, all our tumor cases were submitted to RRP.

In our population, only serum PSA and not CgA or IGF-1 levels were significantly higher in the PCa than in the BPH group. On the contrary, only CgA and not IGF-1 or PSA levels were significantly influenced by the tumor Gleason score and pathological T stage. Considering only pT3 or Gleason score $\geq 7(4+3)$ cases, differences between BPH and PCa groups became significant for CgA whereas the results did not change for PSA and IGF-1. According to our experience, Marszalek et al. [13] did not find significant variations either in CgA or IGF-1 levels between PCa and control cases. Differently to our results,

in their population not only IGF-1 but also CgA levels revealed no significant variations according to the tumor Gleason score. The same authors underlined some limits of their approach [13]: first, their PCa cases were not submitted to RRP and therefore the Gleason score obtained at biopsy was not confirmed after surgery; second, they had no possibility to analyze the results in terms of the pathological T stage. As in the study of Marszalek et al. [13], in our population IGF-1 serum levels do not appear to be significantly related to either the diagnosis or to the aggressiveness of PCa. The negative findings of our study are in line with the majority of series suggesting that IGF-1 serum levels provide no relevant information [13, 14–17]. One potential limit of our approach is that in this population the serum results have not been verified as in previous studies [1, 18] at a tissue level through the mRNA expression with RT-PCR of the three peptides. Previously [1, 18] we showed a significant correlation between serum and tissue expression of CgA in clinically localized PCa submitted to RRP. There is increasing evidence in the literature that CgA might play a role as a marker for advanced PCa, particularly under androgen deprivation and during the hormone refractory phase of the disease [7]. However, also in the non-metastatic phase of the disease, CgA expression correlates with the aggressiveness of the tumor and may provide useful predictive information.

Conclusions

Our data suggest that in clinically localized PCa, the quantification of PSA and CgA serum levels and not of IGF-1 may provide independent significant information in the diagnosis and aggressiveness of PCa, respectively.

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