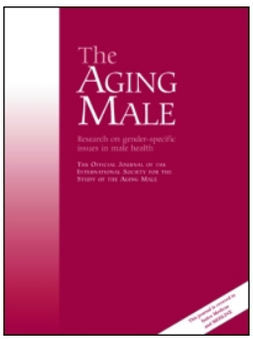

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ORIGINAL ARTICLE

Complex relationship between sex hormones, insulin resistance and leptin in men with and without prostatic disease

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Abstract

Objectives: To assess sex hormones, leptin and insulin-resistance in men with prostate cancer (PCa) and benign prostatic hyperplasia (BPH) and to study associations between androgens and histologic score of prostate tissue in PCa.

Subjects and methods: Two hundred ten men older than 45 years selected from 2906 participants of a population screening for PCa were studied: 70 with PCa, 70 with BPH and 70 controls (CG), matched by body mass index and age. Insulin, IGF-1, PSA, leptin, total, free (fT) and bioavailable testosterone (bT) and estradiol were measured. Each group was subdivided into two subgroups considering the presence of metabolic syndrome (MS); androgens and leptin levels were analyzed in the subgroups.

Results: Prostate cancer and BPH patients presented higher total, fT and bT levels than CG. IGF-1, insulin and HOMA index were higher in BPH than in the other two groups. PCa presented higher leptin [median (range) 6.5 (1.3–28.0) versus 4.8 (1.1–12.3) ng/ml; $p < 0.01$] and estradiol [median (range) 37.0 (20–90) versus 29.0 (20–118) pg/ml; $p = 0.025$] levels than CG. After dividing men considering the presence of MS, leptin was higher and total testosterone was lower in MS patients in all the groups.

Conclusions: It was observed a coexistence of an altered hormone profile with increased sex hormones and leptin in PCa patients, in accordance with the new perspective of PCa pathogenesis.

Keywords

Sex hormones, leptin, prostatic diseases

History

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Introduction

Prostate cancer (PCa) is one of the most common causes of death from cancer in men [1], after lung and colon cancer [2,3]. A large prospective study performed by the American Cancer Society concluded that 14% of cancer deaths of different etiologies are due to obesity [4]. Obesity, in particular abdominal obesity, is commonly associated to different chronic conditions such as cardiovascular disease, metabolic syndrome (MS), diabetes and also some types of hormone-dependent cancers [5]. Regarding PCa, most published studies describe an association between obesity degree and tumor progression, but not between obesity degree and tumor development, highlighting the current controversy in this topic [6–10]. Furthermore, insulin resistance (IR) increases the risk of developing different types of cancer [11] and it has been proposed as a main factor linking obesity and PCa.

Expanded and macrophage infiltrated abdominal adipose tissue is in turn an important source of hormones and cytokines, in particular bioactive peptides such as leptin [12]. Leptin secretion by adipocytes is directly regulated by hormones such as glucocorticoids [13], estrogens [14] and insulin [15]. Previous studies reported that leptin promotes cellular metastasis, as well as endothelial and epithelial cells proliferation and migration, angiogenesis and apoptosis inhibition [16].

Some authors reported that leptin levels increase as well as adiponectin decreases in PCa patients [17–19]. Leptin acts favoring cellular metastasis, as well as endothelial and epithelial cells proliferation and migration, angiogenesis and apoptosis inhibition [16]. It has been suggested that leptin can interact with markers related to abdominal obesity, such as sex hormones and IGF-1, increasing PCa risk [16]. In a previous study, we have shown that in patients with PCa, abdominal obesity impacts on sex hormones and the

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inflammatory profile, with decreased sex hormone-binding globulin (SHBG) and adiponectin levels as well as increased estrogens, free androgens and high-sensitive C-reactive protein levels, independently of body mass index (BMI) [20]. These alterations justify studying the role of abdominal obesity in middle age men.

Benign prostate hyperplasia (BPH) is a highly prevalent disease in men older than 50 years, as result of non-malignant prostate growth, although its etiology is not well known [21]. Previous causal models have focused primarily on sex steroid hormones; however, accumulating evidence indicates that modifiable risk factors might also increase the risk of BPH and potentially contribute to its development [22]. Obesity, elevated fasting plasma glucose levels, diabetes and the MS have been associated with an increased risk of BPH [23]. However, it has also been reported no associations between BMI and BPH in old men [22].

The aim of this study was to assess sex hormone profile, leptin levels and insulin-resistance in three groups of middle age men, matched by BMI and age: men with PCa, BPH patients and a control group (CG) of men with low risk of PCa. An additional objective was to study associations between androgenic hormones and histologic score of prostate tissue in PCa patients.

Subjects and methods

This is a cross-sectional study where a total number of 2906 Caucasians men older than 45 years completed a prostatic evaluation at the Urology Division, Hospital de Clínicas ''José de San Martín'', University of Buenos Aires, in the context of a population screening for the early detection of PCa. Blood samples were obtained by venipuncture after 12-h fasting, digital rectal examination (DRE) was performed in all of them and biomedical measures as weight, height, waist circumference and blood pressure (BP) were determined as well.

Diagnostic criteria for prostatic disease

In those patients with abnormal DRE and/or total PSA (tPSA) $\geq$2.5 ng/ml, a transrectal prostatic biopsy guided by ultrasound was performed, followed by a histological study. According to the results of this study men were divided into two groups: BPH (prostatic adenoma, $n = 70$) and PCa (prostatic adenocarcinoma, $n = 70$). A CG included 70 men with low risk of PCa, with tPSA <2.50 ng/ml and normal DRE, without indication of transrectal ultrasound and biopsy and with no family history of PCa.

PCa patients were classified according to Gleason system score [24]. The selection of subject members of groups BPH and CG was conducted among men who attended the same day and at random among men with BMI and age matched with PCa group.

Participants were asked about family history of neoplasia, diet, cigarette smoking and medication.

Exclusion criteria: presence of other neoplasias, previous prostatic disease and/or hormonal therapy, alcohol consumption >20 g/day, drugs modifying lipid metabolism.

The study was conducted using Good Clinical Practices and patients gave their informed consent about purposes of the study. Both the study protocol and the informed consent were evaluated and approved by the Ethics Committee of the University Clinical Hospital of Buenos Aires and the study was conducted in accordance with the ethical principles that have their origins in the World Medical Association Declaration of Helsinki.

Biomedical parameters

Waist circumference (WC) was measured as an indicator of abdominal obesity, at the level midway between the lateral lower rib margin and the superior anterior iliac crest, in a standing position. In order to calculate the BMI, weight and height were obtained for each patient.

Blood pressure was registered in sitting position, after 10-min resting. The sphygmomanometer was applied to the left and right arm, and a median of the values obtained was calculated. Systolic and diastolic blood pressures (SBP and DBP) were determined.

Metabolic syndrome diagnosis

The MS was diagnosed according to the National Cholesterol Education Program (NCEP), Adult Treatment Panel-III (ATP III) [25]. Patients were classified as having MS if they met three or more of the following criteria: WC > 102 cm, TG $\geq$ 1.7 mmol/l, HDL cholesterol < 1.03 mmol/l, SBP and/or DBP $\geq$ 130/85 mmHg, and fasting glucose $\geq$ 6.1 mmol/l.

Insulin resistance diagnosis

It was determined through the HOMA (Homeostasis Model Assessment of Insulin Sensitivity) index [26]: Insulin mUI/l $\times$ glucose mmol/l/22.5.

Analytical methods

The following measurements were performed in serum samples: tPSA was determined by a chemoluminiscent immunometric method (Immulite 1 autoanalyzer, Siemens Healthcare Diagnostics Products Ltd, UK) The intra-assay (CVi) and interassay (CVe) variation coefficients for PSA were 3.98 and 4.31, respectively.

Insulin was measured by a coated tube radioimmunoassay (RIA) (Diagnostics Products Corporation, Los Angeles). Results are expressed in μU/ml. CVi and CVe were <10% in all the concentration range studied.

IGF-1 was determined by a chemoluminiscent immunometric method (Immulite 1 autoanalyzer, Siemens Healthcare Diagnostics Products Ltd, UK) Results are expressed in ng/ml. The detection limit for IGF-1 was 20 ng/ml and CVi and CVe were 4.3% and 8.4%, respectively.

Total testosterone (TT) and SHBG were performed by enzymatic chemoluminiscent methods, competitive and non-competitive, respectively (Immulite 1 autoanalyzer, Siemens Healthcare Diagnostics Products Ltd, UK), CVi <7% and CVe <12% for To and CVi <8% and CVe <13.5% for SHBG.

Free testosterone (fT) and bioavailable testosterone (bT) were calculated from TT and SHBG, according to Vermeulen equation [27].

Estradiol was measured by a competitive chemoluminiscent immunoassay (Immulite 1 autoanalyzer, Siemens

Table 1. General characteristics of the study population.

	CG ($n = 70$)	BPH ($n = 70$)	PCa ($n = 70$)
Age (years)	62 (53–75)	62 (45–76)	65 (49–75)
BMI (kg/m^2)	26.2 (19.6–40.4)	26.8 (19.8–36.7)	27.4 (19.0–38.8)
WC (cm)	99 ± 10	99 ± 10	102 ± 11
SBP	140 (100–210)	140 (100–180)	140 (110–200)
DBP	80 (70–120)	80 (60–110)	80 (60–110)
tPSA (ng/ml)	0.99 (0.17–2.44)*	4.33 (0.60–50.10)**	7.09 (0.11–150)

Results are expressed as median (range) or mean ± SD, according to data distribution. CG, control group; BPH, benign prostatic hyperplasia; PCa, prostate cancer; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; tPSA, total prostate-specific antigen.
Kruskal–Wallis *$p < 0.001$ versus BPH and CaP; **$p < 0.05$ versus CG and PCa.

Table 2. Sex hormone profile in the three studied groups.

	CG ($n = 70$)	BPH ($n = 70$)	PCa ($n = 70$)
TT (nmol/l)	15.3 (6.9–35.7)*	18.4 (8.7–35.4)	17.7 (6.2–44.7)
fT (pmol/l)	263.1 (100.5–700.3)**	302.7 (160.2–839.0)	311.0 (105.4–811.3)
bT (nmol/l)	6.07 (2.32–16.16)***	6.97 (3.68–19.31)	7.14 (2.43–18.69)
SHBG (nmol/l)	44.4 (2.0–102)	46.3 (14.3–122)	42.7 (9.3–126)
E2 (pmol/l)	106.5 (73.4–433.2)	79.3 (73.4–301.0)	135.8 (73.4–330.4)****

Results are expressed as median (range). CG, control group; BPH, prostatic benign hyperplasia; PCa, prostate cancer; TT, total testosterone; fT, free testosterone; bT, bioavailable testosterone; SHBG, sex hormone-binding globulin; E2, estradiol.
Kruskal–Wallis test *$p < 0.01$ versus BPH and PCa, **$p < 0.026$ versus BPH and PCa, ***$p < 0.025$ versus BPH and PCa, ****$p < 0.025$ versus BPH and CG.

Table 3. IR parameters and IGF 1.

	CG ($n = 70$)	BPH ($n = 70$)	PCa ($n = 70$)
Insulin (μUI/ml)	5.8 (0.3–23.7)	8.4 (1.7–24.5)*	5.0 (0.3–39.2)
IGF-1 (ng/ml)	143 (54–336)	164 (67–390)**	132 (69–241)
HOMA	1.8 (0.1–16.0)	2.1 (0.4–11.0)***	1.3 (0.06–11.0)

Results are expressed as median (range). CG, control group; BPH, prostatic benign hyperplasia; PCa, prostate cancer; IGF-1, insulin-like growth factor 1; HOMA, Homeostasis Model Assessment of Insulin Sensitivity; IR, insulin resistance.
Kruskal–Wallis test *$p = 0.001$ versus CG and PCa, **$p = 0.007$ versus CG and PCa, ***$p = 0.003$ versus PCa.

Healthcare Diagnostics Products Ltd, UK), CVi <9.5% and CVe <11% in all the concentration range studied.

Leptin was determined by RIA (Millipore Corporation, Billerica, MA), CVi and CVe <6.2% in all the concentration range studied.

Statistical analysis

In order to evaluate differences between groups parametric and non-parametric methods were used, according to data distribution. Variables with a normal distribution were studied through ANOVA and Scheffé post-test and for variables with a non-parametric distribution, Kruskal–Wallis test and Dunn post-test were used. When two groups were compared, Mann–Whitney test was applied; $p < 0.05$ was considered statistically significant. Statistical analysis was performed using SPSS 19 software (Chicago, IL) and Infostat (Córdoba, Argentina).

Results

As seen in Table 1, main characteristics of the study population were evaluated: age, BMI, WC, SBP, DBP and tPSA. Mean age of men in this study was >60 years old (45–76 years). There were no significant differences between groups in WC, SBP and DBP. As it was expected, tPSA levels were significantly lower in CG than in BPH and PCa groups (median 0.99 versus 4.33 and 7.09 ng/ml, respectively).

Sex hormones profile was evaluated in the three groups. PCa and BPH patients presented higher TT, fT and bT levels than CG (Table 2). SHBG concentrations were not significantly different among the three studied groups. Estradiol was higher in PCa when compared with BPH and CG (Table 2).

IGF-1 and IR surrogate markers (insulin and HOMA index) were higher in BPH group than in the other two groups of patients (Table 3).

When leptin levels were measured in the three groups it was found that in PCa group was significantly higher than in CG (median (range) 6.5 (1.3–28.0) versus 4.8 (1.1–12.3) ng/ml; $p < 0.01$).

Each group was subdivided into two subgroups considering the presence of MS; then androgens and leptin levels were analyzed in the subgroups. Leptin levels were higher and TT was lower in those patients with MS, in the three groups. SHBG showed differences only in BPH patients, being lower in MS subgroup. Additionally, fT and bT only diminished in PCa patients with MS (Table 4).

Table 4. Hormonal profile and leptin levels in the three groups studied.

Group	MS	Leptin (ng/ml)	TT (nmol/l)	SHBG (nmol/l)	fT (pmol/l)	bT (nmol/l)
CG	No ($n=49$)	4.2 (1.1–8.9)	16.1 (8.3–35.7)	45.5 (2.0–102)	269.4 (100.5–669.1)	6.21 (2.32–15.25)
	Yes ($n=21$)	6.9 (3.7–12.3)[a]	13.4 (6.9–25.3)[c]	44.7 (7.2–99.3)	236.1 (118.2–700.3)	5.54 (2.77–16.16)
BPH	No ($n=54$)	4.1 (0.8–17.4)	19.1 (8.7–35.4)	50.9 (14.3–122)	307.9 (160.2–839.0)	7.07 (3.67–19.31)
	Yes ($n=16$)	10.2 (3.5–23.6)[b]	14.6 (8.7–27.4)[d]	29.8 (22.8–81.5)[c]	294.0 (174.0–405.6)	6.76 (3.99–9.36)
PCa	No ($n=50$)	5.7 (1.3–28)	19.8 (6.2–44.7)	44.2 (15.8–126)	366.8 (105.4–811.3)	8.42 (2.43–18.69)
	Yes ($n=20$)	8.0 (4–17)[c]	14.7 (6.6–35.7)[e]	38.2 (9.3–94.1)	253.1 (138.3–773.1)[f]	5.82 (3.19–17.79)[c]

The three groups were subdivided according to the presence (''Yes'') or absence (''No'') of MS. Results are expressed as median (range). CG, control group; BPH, prostatic benign hyperplasia; PCa, prostate cancer; TT, total testosterone; fT, free testosterone; bT, bioavailable testosterone; SHBG, sex hormone-binding globulin.
Mann–Whitney test, MS ''Yes'' versus MS ''No'' in each group: [a]$p=0.001$, [b]$p=0.003$, [c]$p=0.006$, [d]$p=0.046$, [e]$p=0.01$, [f]$p=0.029$.

Table 5. Androgenic profile in relation to tumor grade.

Tumor grade	TT (nmol/l)	fT (pmol/l)	bT (nmol/l)	SHBG (nmol/l)
Moderately differentiated ($n=58$)	19.4 (6.2–44.7)	339.8 (138.7–1112.9)	7.63 (3.12–25.66)	42 (2–94)
Poorly differentiated ($n=12$)	15.2 (8.7–26.3)	221.9 (104.0–436.8)*	5.20 (2.43–10.05)*	53 (35–126)

Results are expressed as median (range). Mann–Whitney test, *$p=0.02$ versus moderately differentiated.
TT, total testosterone; fT, free testosterone; bT, bioavailable testosterone; SHBG, sex hormone-binding globulin.

In order to evaluate differences in sex hormones profile in relation to the tumor grade, PCa patients were divided considering histological differentiation according to the Gleason *score*: moderately differentiated 6 (3 + 3) and 7 (3 + 4), and poorly differentiated 7 (4 + 3) and ≥8. TT, SHBG and IGF-1 levels were similar in patients with moderately and poorly differentiated tumors, while fT and bT were significantly lower in the second subgroup (Table 5).

Discussion

In this study sex hormones, IR surrogate markers and leptin levels were evaluated in men with BPH, PCa and a group of men with low risk of PCa with similar age and BMI. Sex hormones were increased in PCa patients compared with CG patients, meanwhile IR surrogate markers were higher in BPH patients than in CG and PCa patients, and finally leptin levels were higher in PCa and BPH patients.

Given the hormone-dependent characteristics of this tumor, sex hormones profile has been studied in PCa patients. The relationship between testosterone levels and PCa is controversial. Some authors find that PCa is associated either with low or high testosterone levels [28–31]. Even more, low TT concentrations are associated with higher severity and lower differentiation of prostatic tumors [32,33]. However, it has also been reported that lower TT levels are related to a decrease in disease progression [34]. In this study, mean values of testosterone and its subfractions were higher in BPH and PCa compared with CG, even more, we found higher estradiol levels in PCa patients. Other authors suggest that sex steroid hormones, specifically the estrogen–androgen balance, may be important in the development of aggressive PCa [35]. Williams et al. [36] proposed that intracellular estradiol levels are responsible of inducing and promoting obesity, MS, BPH and PCa in men, rather than testosterone decline. This point can be explained by a greater conversion of TT to estradiol, which in turn inhibits luteinizing hormone by negative feedback and consequently diminishes testosterone synthesis. Although in this study TT levels were higher in PCa group, it must be considered that studies in which PCa patients show low TT levels correspond to patients with more advanced tumors and high Gleason score. We found that 83% of patients showed early tumor stages, as it is expected in a population screening for the early detection of PCa. Nevertheless, when PCa patients were subdivided considering tumor differentiation degree, fT and bT, biologically active fractions of testosterone, were lower in men with more advanced tumors, in accordance with findings from other authors [37,38].

Stocks et al. [39] observed that androgens have a role in early PCa development, while IR-related factors could be important for tumor progression in PCa patients. It has also been reported that metabolic alterations could promote BPH and PCa pathogenesis [23]. Our results show that insulin, HOMA index and IGF-1 were higher in BPH patients when compared with CG and PCa group. This association could be explained considering that higher IGF-1 concentrations increase and regulate cell proliferation and differentiation [40]. Besides, in patients with MS, IR and the subsequent hyperinsulinemia are related with higher PCa risk [41].

The hypothesis considering that high leptin concentrations can influence evolution from latent PCa to a clinically detectable entity, is biologically possible. *In vitro* and *in vivo* studies show that this adipokine could promote angiogenesis, being an important factor for growing and dissemination of various kinds of neoplasias, including PCa [42,43]. These studies suggest that leptin should act as a promoter of tumor growth, favoring angiogenesis, vascular cells proliferation and inhibiting apoptosis, allowing progression, invasion and metastasis [43]. Singh et al. evaluated the relationship between leptin and PCa, and its association with obesity. These authors demonstrated that PCa is associated with higher leptin levels, independently of obesity and PSA [44]. These findings are in accordance with our results, we found

that mean leptin values were higher in PCa patients compared with CG.

After subdividing each group considering the presence of MS, it was found that the number of subjects with MS was similar in the three groups. Some investigators report that MS patients should be at greater risk of having high PCa grade tumors [45]. Nevertheless, in the three groups studied, subjects with MS showed higher leptin levels and lower TT concentrations, suggesting that MS could be another risk factor to consider in prostatic health evaluation. Furthermore, only PCa patients with MS showed lower levels of biologically active fractions of testosterone, and SHBG only decreased in men with BPH and MS.

In contrast with other authors who find higher IGF-1 values in patients with moderately differentiated tumors [46], in this article, IGF-1 levels were not significantly different between groups.

This study presents some limitations, such as the number of patients in each group, the lack of patients' follow-up and the fact that it was not possible for us to determine IGFBP-3 levels, which it would have been interesting. However, the fact that the groups are matched by age and BMI reflects a strength in the design.

Conclusion

The hypothesis that considers testosterone as the main responsible of PCa development should include a more complex hormonal relationships, which enhance estradiol effect in prostate cells proliferation. In this study, it was observed a coexistence of an altered hormone profile, with increased estradiol and leptin levels in PCa patients that is in accordance with the new perspective of PCa pathogenesis. Leptin would be part of the development of prostatic pathology in patients with MS. This could imply the need for earlier controls in these patients. However, more studies are required in patients with this disease, which must consider the inclusion of subjects with genetic, ethnic and environmental identity.

Declaration of interest

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