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ORIGINAL PAPER

Leptin increases prostate cancer aggressiveness

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Abstract Recent studies indicate that adipose tissue and adipocytokines might affect the development of prostate cancer (PCa). Leptin would have a stimulating effect on prostate cancer cells by inducing promotion and progression, whereas adiponectin would have a protective effect. The aim of this study was to determine the relation between body composition, leptin, and adiponectin levels with the prevalence and aggressiveness of PCa in men of Mendoza, Argentina. Seventy volunteers between 50 and 80 years (35 healthy men as control group and 35 with PCa) were selected. The PCa group was subclassified according to the Gleason Score (GS). Digital rectal examination, transrectal ultrasound, and prostatic biopsy were performed; PSA, testosterone, leptin, and adiponectin levels were determined; and a nutritional interview including anthropometric measurements and a food frequency questionnaire was carried out. Statistical analysis was performed by Student *t* test, ANOVA I, and Bonferroni ($p<0.05$). Body mass index and percentage of body fat mass were not statistically different between PCa and control groups. However, body fat mass was higher in subjects with more aggressive tumors ($p=0.032$). No differences were observed regarding leptin levels between the groups. Nevertheless, leptin levels were higher in subjects with high GS ($p<0.001$). Adiponectin levels showed no statistical differences regarding the presence and aggressiveness of the tumor ($p=0.131$). Finally, consumption and nutrient intake did not differ in the studied groups. In conclusion, body composition and leptin are related to the PCa aggressiveness but not with its prevalence.

Keywords Leptin · Adiponectin · Body mass index · Prostate cancer prevalence

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Introduction

Obesity, defined as an excessive energy accumulation as fat in the organism, is acquiring the characteristics of an authentic pandemia. It represents one of the major current challenges for world public health since it entails a

disease with serious consequences on obese people's health [12, 51]. The impact of overweight on the cardiovascular, respiratory, digestive, osteoarticular, reproductive, and endocrine-metabolic systems are very well known as well as its relation to several types of cancer, including prostate cancer (PCa) [8].

Although epidemiological studies underline that obesity represents a significant risk factor for the development of PCa, the exact mechanism of this relationship remains to be determined. Leptin and adiponectin may participate in a molecular pathway whereby obesity exerts its effects on prostate tumor biology. Most studies indicate that, while leptin may potentiate the growth of cancer cells in vitro, adiponectin appears to have an opposite effect [20, 27].

Leptin is a peptide of 167 amino acids with a molecular weight of 16 kDa and encoded by the *Ob* gene. Its synthesis occurs mainly in white adipose tissue and to a lesser extent in the placenta, skeletal muscle, stomach, and mammary gland epithelium [34]. Leptin levels are positively correlated with total body fat, nutritional status, and triglyceride content of adipocytes. Thus, serum leptin levels are elevated in obese subjects compared to individuals with normal weight, acting as a "marker" of the body's energy reserves [5]. Recent studies suggest that leptin could be a promoting factor of tumor growth by inducing angiogenesis and the proliferation of vascular cells and, in this way, favoring tumor progression, invasion, and metastasis [48]. Also, leptin may affect PCa growth via obesity-related factors such as testosterone, IGF-1, and VEGF, and influence cell differentiation and PCa progression.

Adiponectin is a 244 amino acid protein with a molecular weight of 30 kDa, produced exclusively by the white adipose tissue [33]. Opposite to other adipocytokines, its circulating levels are inversely correlated to obesity (particularly central obesity), body mass index (BMI), accumulation of visceral fat, and insulin resistance [33]. It has been described as the "anticancer" adipokine, including anti-PCa [10]. Recent studies have found plasma adiponectin levels to be significantly lower in patients with PCa than in those with benign prostate hyperplasia (BPH) and control subjects [20]. In addition, these studies have documented a negative association between adiponectin, Gleason Score (GS) and disease stage [20].

Therefore, the aim of the present study was to determine the relation between body composition, leptin, and adiponectin levels with the prevalence and aggressiveness of PCa in men of Mendoza, Argentina.

Methods and materials

Subjects

A sample of 70 volunteers between 50 and 80 years old (35 healthy men as control group and 35 with PCa) was selected for the study, according to the inclusion and exclusion criteria described in Table 1. Moreover, the PCa group was subclassified regarding the GS.

The subjects participated in the study after giving a written consent, which was approved by the Local Ethical Committee at Universidad Nacional de Cuyo, Mendoza, Argentina.

Table 1 Inclusion and exclusion criteria used in the study

Inclusion criteria	Exclusion criteria
Age 50–80 years	Other urological tumors
BMI >25 kg/m^2	Prostatic nodules
PCa recently diagnosed	History of HGPIN and/or ASAP
Not on medication/s known to alter serum PSA	Old PCa treated
No prostate, endocrine, or metabolic disease	Elevated PSA with repeated negative prostate biopsies
Less than ±3 kg variation in body weight within the last 3 months	Patients with indwelling catheter
	Participation in another research study or nutritional intervention within the last 3 months

HGPIN high-grade prostatic intraepithelial neoplasia, *ASAP* atypical small acinar proliferation

Experimental design

The study included a *urological examination*, a *nutritional interview*, and *laboratory tests.*

Urological examination A urologist performed a digital rectal examination (DRE), measurement of prostate volume by transrectal ultrasound, and ultrasound-guided prostate biopsy. Prostate gland volume was calculated with the prolate ellipsoid formula using a 6.5-MHz biplanar endorectal transducer in all patients. In cases of suspected tumor, a puncture needle was introduced, and sextant biopsies were obtained with cylinders of 1.5 cm (12–14 cores). Paraffin inclusions of the biopsies were cut at 5 μm thick and stained with hematoxylin and eosin (H&E) for the histological study and the estimation of GS in subjects with PCa. High-grade PCa was defined by a GS of 8 or higher, intermediate-grade PCa by a GS of 7, and a low-grade PCa by a GS of 6 or less.

Nutritional interview The volunteers attended a nutritional interview, during which a detailed dietary history was performed and a food frequency questionnaire was completed. The food frequency questionnaire used in this study has been adapted from those used in two large American cohorts, the Nurses' Health Study and the Health Professionals' Follow-up Study [11, 50]. Data from food records were used to calculate intakes of total energy and macronutrients with a computer program based on Argentinean food tables specially designed for the study.

Body composition was determined by direct anthropometric determinations including height, weight, waist and hip circumference, arm perimeter, and skinfold thickness. All of them were assessed three times by the same trained dietitian, and the mean value was recorded [17]. Participants wore a hospital gown or other light clothing, and did not wear shoes during the anthropometric determinations.

BMI was calculated as weight (in kilogram) divided by the square of the height (in meter). Waist/hip circumference ratio (WHR) was calculated as waist circumference (in centimeter) divided by the hip circumference (in centimeter). Skinfold thickness sum was calculated adding the tricipital, bicipital, subscapular, and suprailiac skinfold thickness measured with a caliper (Holtain Ltd. Crymech, UK). The arm perimeter and the skinfold thickness were used to estimate the body fat mass (in gram) and the body free fat mass (in gram). Each of them was expressed as a percentage of the total body weight (percent).

Laboratory tests Ten milliliters of venous blood was collected from each patient. Blood was allowed to clot at room temperature, and serum was separated and stored at −20°C until assayed. Serum total PSA concentration was measured by a Microparticle Enzyme Immunoassay method (MEIA) using the Abbott IMX™ system (Abbott Laboratories, Abbott Park, IL). Leptin and adiponectin were measured by an enzyme-linked immunosorbent assay (ELISA) using a manual kit provided by Linco Research, Inc. Serum testosterone was determined by an electrochemiluminescence immunoassay method using the Siemens Advia Centaur™ system (Siemens Healthcare Diagnostics, Deerfiled, IL).

Statistical analysis

Values are given as means ± SEM. The statistical analysis was performed using SPSS 15.0 software (SPSS Inc., Chicago, IL). Differences in the distribution of several nutritional, anthropometric, and metabolic related variables in the two studied groups (PCa and control) were assessed using Student's t test or Mann–Whitney U test regarding the normality of the variables as evaluated by the Kolmogorov–Smirnov test. When comparisons were made among groups with different GS, ANOVA I or Kruskal–Wallis' test were used. Post hoc comparisons between means were made by Bonferroni–Dunn test. The level of significance was determined at $p<0.05$.

Results

The study sample included 35 control subjects and 35 subjects with PCa, which also were subdivided according to the tumor aggressiveness using the GS: low GS ($n=12$), intermediate GS ($n=14$), and high GS ($n=9$). Prostate volume, PSA, and testosterone levels were similar among the studied groups. BMI, WHR, and percentage of body fat mass were not statistically different between the PCa and the control group. However, subjects with more aggressive tumors had more body fat mass than those with lower GS ($p=0.032$) (Table 2).

Table 2 Anthropometrical and urological characteristics of subjects from the different groups studied

	PCa	Control	p^a	GS			p^b
				Low	Intermediate	High	
n	35	35		12	14	9	
Age (year)	63.76±0.85	64.88±1.32	0.507	65.55±2.49	64.92±1.92	63.25±2.83	0.835
PSA (ng/ml)	6.06±1.97	1.10±0.15	0.032#	3.23±1.34	8.58±3.6	3.59±1.29	0.056
Prostate volume (cc)	57.57±9.90	35.64±5.32	0.168	47.25±8.91	64.95±18.99	56.07±9.47	0.45
Testosterone (ng/ml)	4.59±0.51	4.62±0.21	0.959	4.13±0.4	5.28±0.88	3.21±0.93	0.284
Weight (kg)	96.98±4.25	91.0±2.54	0.212	83.8±3.68	93.26±3.65	98.02±5.59	0.228
BMI (kg/m^2)	31.74±1.15	30.8±0.68	0.47	30.00±1.22	30.51±0.94	33.55±1.47	0.477
Waist circumference (cm)	110.06±3.42	108.24±2.06	0.633	103.03±2.77	109.05±3.19	116.0±2.27	0.360
Hip circumference (cm)	109.52±2.69	109.5±1.64	0.996	105.35±2.93	110.37±2.31	115.0±2.04	0.430
WHR	1.00±0.02	0.98±0.01	0.366	0.98±0.01	0.98±0.02	1.01±0.01	0.692
Arm perimeter (cm)	35.38±1.04	33.62±0.55	0.119	33.2±0.98	33.27±0.78	35.62±1.07	0.284
Triceps skinfold thickness (mm)	16.98±2.19	15.72±1.09	0.582	14.06±1.82	15.0±1.22	21.3±3.6	0.379
Skinfold thickness sum (mm)	76.05±10.12	70.56±1.16	0.398	62.41±7.5	67.89±4.89	95.53±5.69	0.420
Free fat mass percentage (%)	67.56±1.31	67.95±1.08	0.821	68.23±1.6	69.94±1.24	60.89±2.45*	0.032
Body fat percentage (%)	32.44±1.31	32.05±1.08	0.821	31.76±1.6	30.06±1.24	39.11±2.45*	0.032

Values are expressed as mean ± SEM

#$p < 0.05$; PCa subjects compared to their controls

*$p < 0.05$; means are significantly different compared to low and intermediate GS (Bonferroni's test)

[a] Student *t* test or Mann–Whitney *U* test was used to compare the PCa and the control groups

[b] ANOVA I or Kruskal–Wallis' test was used to compare the three levels of GS

Regarding diet composition, both groups showed a similar energy intake (Table 3). Macronutrient distribution in the diet of all volunteers was within normal parameters recommended for the general population: carbohydrates: 50–55% of energy intake; protein: 15–20% of energy intake, lipids: 30–35% of energy intake.

Figure 1 shows serum adipocytokines levels in the different groups. PCa patients had similar leptin levels

Table 3 Macronutrient intake obtained from a detailed dietary history and a food frequency questionnaire

	PCa	Control	p^a	GS			p^b
				Low	Intermediate	High	
Energy intake (kcal/24 h)	2267.14±205.74	2247.7±120.78	0.939	2018.82±385.5	2327.06±311.23	2506.9±329.5	0.799
Protein (g/24 h)	96.89±9.41	97.68±4.74	0.070	84.61±11.27	97.00±14.74	118.05±23.79	0.559
Protein (% of energy intake)	17.38±0.61	17.87±0.9	0.648	17.91±1.15	16.81±0.86	18.35±1.49	0.805
Lipid (g/24 h)	71.55±7.63	76.11±5.49	0.468	69.69±15.49	69.20±10.99	82.42±14.88	0.863
Lipid (% of energy intake)	28.25±1.31	30.39±1.32	0.261	30.29±2.88	26.86±1.69	29.18±3.01	0.441
Carbohydrate (g/24 h)	256.98±27.48	254.6±19.19	0.946	207.8±49.91	272.97±41.78	292.02±35.01	0.600
Carbohydrate (% of energy intake)	44.56±1.83	44.8±1.6	0.922	39.36±2.96	46.5±2.45	47.37±4.84	0.253

Values are expressed as mean ± SEM

[a] Student *t* or Mann–Whitney *U* test

[b] ANOVA I or Kruskal–Wallis' test

than healthy subjects. Interestingly, leptin levels were higher in subjects with high GS (12.1±3.01 ng/ml) compared with those with intermediate (3.83±0.61) and low GS (2.60±0.41 ng/ml) ($p<0.0001$) (Fig. 1a), in agreement with the major fat mass percentage observed in this group. Finally, adiponectin levels showed no statistical differences regarding the presence and aggressiveness of the tumor (Fig. 1b).

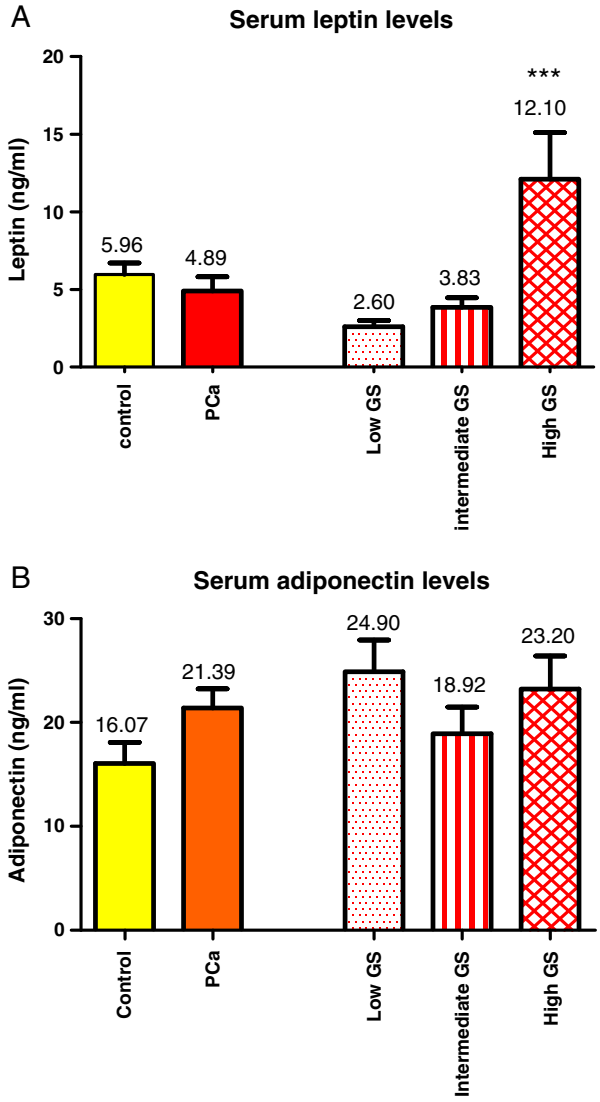

Fig. 1 Adipocytokines circulating levels of subjects from the different groups studied. **a** Serum leptin levels of control and prostate cancer (*PCa*) subjects (*left*), and of those with PCa subclassified according to the Gleason Score (*GS*) (*right*). Values are expressed as mean ± SEM. ***$p<0.0001$ compared with low and intermediate GS groups (Bonferroni's test). **b** Serum adiponectin levels of control and PCa subjects (*left*) and of those from the three levels of GS (*right*). Values are expressed as mean ± SEM

Discussion

Even though some epidemiologic [1, 6, 16, 30] studies have suggested a relationship between obesity and PCa, a direct cause–effect link between these two variables has not been conclusively demonstrated by others [15]. This disagreement may lie in that not only is obesity an excess of body fat but it also alters several physiological parameters that may affect PCa including testosterone, estrogen, insulin, IGF-1, leptin, and adiponectin [1, 6, 16, 30, 39]. Lower sex hormone-binding globulin in obese patients may increase free dihydrotestosterone (DHT) [1, 37], which acts as a stimulatory factor on the prostate epithelium. Elevated serum insulin and IGF-1 concentrations in obese patients may facilitate progression of PCa [37]. Leptin is elevated and adiponectin diminished in obese men [39]. In addition, obesity is highly correlated with diet in terms of total energy intake as well as the amount of dietary fat, both of which have been linked to cancer [43].

PCa incidence and mortality rates are associated with Western lifestyle and diet. Several epidemiologic studies have investigated the relationship between dietary fat intake and human PCa [28, 43]. Most case–control studies have demonstrated a positive relationship between dietary fat intake and PCa risk [35]. However, some of those studies have the limitation of recall bias: dietary recall can result in inaccurate information about true exposure history [18, 49]. Our results showed no statistically significant association between dietary fat, energy intake, and PCa risk in agreement to several prospective cohort studies in which dietary data recall is more accurately assessed [19, 22, 32, 37, 44, 45]. Even when the relationship between fat intake and PCa risk is controversial, a link with advanced disease and mortality is currently accepted [31, 46].

Similarly, the majority of the epidemiologic bibliography suggests that obesity may be related to the risk of PCa, but it is more clearly associated with an increased risk of dying from PCa [4, 9, 40, 46]. Two large multi-institutional studies observed that obese men were at increased risk of biochemical failure [3, 14]. Many studies have found that men with an

augmented BMI had higher-grade and/or higher-stage disease [2, 36, 41]. Accordingly, our results show that BMI and body fat mass are elevated in those volunteers with a high GS.

On the other hand, WHR provides an estimate of abdominal obesity associated to various hormonal and metabolic disorders, as well as to the risk of other comorbid diseases, such as heart disease, diabetes, and cancer [26]. Although a few studies have examined WHR regarding PCa [21], WHR may be more closely related to the development of PCa than BMI or fat mass [15]. However, we did not find a significant relationship between PCa risk, aggressiveness, and WHR in this study.

Numerous studies have investigated the relation between obesity, leptin, and PCa [10, 15, 23, 47]. High levels of leptin have been significantly correlated with testosterone and PSA levels in subjects with PCa compared with subjects with BPH and the control group [42].

Chang et al. reported that high leptin concentrations are positively associated to the volume of the tumors [15]. Saglam et al. observed that a leptin increase is related to an advanced stage of the illness and to a poorly differentiated tumor [42]. Interestingly, our results showed that volunteers with high-grade cancer had higher levels of leptin and BMI than those with lower-grade cancer, supporting previous studies [15, 42].

The hypothesis that high leptin concentrations influence the evolution of a latent PCa to a clinically detectable one is biologically feasible. In vitro and in vivo studies show that this adipokine could promote angiogenesis as a determining factor for the growth and spreading of several types of cancers including PCa [5, 48]. Also, leptin could increase other cytokines and growth factors such as VEGF which is involved in tumor transformation [13].

Finally, obesity is associated with decreased serum adiponectin. Although the role of adiponectin in cancer is poorly understood, one study [45] suggested that adiponectin has antiangiogenic properties. More recent studies have shown that adiponectin has an inhibitory function on the growth of PCa cells and suppresses the proliferation stimulated by leptin, IGF-1, and DHT [7, 24]. It is also demonstrated that adiponectin levels are lower in patients with breast, endometrium, prostate, and colon cancer [38]. One small nested case–control study [25] found no association between adiponectin levels and PCa risk. However, two studies [7, 29] found lower adiponectin levels associated with more advanced or higher-grade PCa. The evidence presented here shows no difference in the adiponectin levels regarding the presence and aggressiveness of the tumor.

In conclusion, the excess of adipose tissue in the organism and serum leptin levels are related to PCa aggressiveness, rather than being risk factors. Adiponectin is not associated with prostate carcinogenesis. Future studies are necessary to clear up even more this relation and, consequently, to develop prevention and early detection measures and new strategies for PCa treatment.

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Conflicts of interest None of the contributing authors has any conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript.

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