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Original article

Cholinesterase activities and biochemical determinations in patients with prostate cancer: Influence of Gleason score, treatment and bone metastasis

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ABSTRACT

Prostate cancer (PCa) is the sixth most common type of cancer worldwide. Cholinesterase is well known as having non-cholinergic functions such as cellular proliferation and differentiation, suggesting a possible influence of cholinesterase in tumorogenesis. Thus, the aim of this study was to investigate the whole blood acetylcholinesterase (AChE) and plasma butyrylcholinesterase (BChE) activities and some biochemical parameters in PCa patients. This study was performed in 66 PCa patients and 40 control subjects. AChE and BChE activities were determined in PCa patients and the influence of the Gleason score; bone metastasis and treatment in the enzyme activities were also verified. Furthermore, we also analyzed possible biochemical alterations in these patients. AChE and BChE activities decreased in PCa patients in relation to the control group and various biochemical changes were observed in these patients. Moreover, Gleason score, metastasis and treatment influenced cholinesterase activities and biochemical determinations. Our results suggest that cholinesterases activities and biochemical parameters are altered in PCa. These facts support the idea that the drop in the cholinesterase activity and the consequent increased amount of acetylcholine could lead to a cholinergic overstimulation and increase the cell proliferation in PCa.

1. Introduction

Prostate cancer (PCa) is an important cause of mortality and morbidity worldwide and it is the most common noncutaneous malignancy in men [1]. The standard prognostic approach to PCa patients includes some clinical and pathological characteristics, such as Gleason score, presence of metastasis and response to hormonal therapy. PCa is a major age-related malignancy with most incidences occurring between 54 and 75 years [2]. The histologic differentiation grade is the strongest prognosticator of PCa. The morphological appearance of cancer cells reflecting distinct degrees of differentiation was elegantly analyzed and classified by Gleason [3,4] into the currently used standard grading system, which is based on the degree of glandular differentiation and the interaction of the malignant glands with stroma.

Little is known about the risk factors for PCa progression [5]. Family history of PCa is a well-established risk factor for PCa risk in men. Several prospective [6] and retrospective [7] studies have reported two to four fold increased risk of PCa in men with a positive family history of PCa especially in a first-degree relative. Many other factors have been studied for their potential role as risk factors for PCa, but the evidence for or against each have been contradictory. These factors have included alcohol use [8], tobacco use [9] and occupation [10]. A large number of studies have assessed the risk of PCa in various occupational groups. There are some hints that occupational groups potentially exposed to pesticides, which include farmers might experience excess risks [10].

Although great advances have been made in the treatment of PCa in recent years, questions still remain concerning the optimal treatment strategy for both localized disease and metastatic disease (mainly bone metastasis). The lack of a standard treatment approach may be partly attributed to variations in the risk of disease progression among patients [11]. Several different hormonal therapies, which act by different mechanisms, are available. Luteinizing hormone-releasing hormone (LHRH) agonists such as goserelin down regulate the pituitary LHRH receptors suppressing the luteinizing hormone (LH) and testosterone

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secretion [12]. The introduction of LHRH agonists revolutionized the treatment of advanced PCa [13].

Increasingly, evidence supports the involvement of cholinesterases in nonclassic functions [14,15], such as cellular proliferation and differentiation [16], suggesting a possible influence of cholinesterases in tumorigenesis. Indeed, either the cholinesterase genes are structurally altered or their products are aberrantly expressed in a variety of tumor types [17–19]. Butyrylcholinesterase (BChE) and acetylcholinesterase (AChE) catalyze the hydrolysis of choline esters. BChE is abundant in liver and plasma [20]. It efficiently hydrolyses butyrylcholine and has a major role in the metabolism of some clinically important anesthetic agents. AChE is found in many tissues, including erythrocytes, nerve endings, lungs, spleen, and brain [21]. It has relative specificity to the neurotransmitter acetylcholine, playing a crucial role in the nervous system function. Although the function of "non-neuronal cholinergic system" is not yet clarified, it appears to intervene in important cell processes such as proliferation, differentiation, apoptosis and cell–cell recognition [22].

In patients with PCa, various biological (family history), biochemical (lactate dehydrogenase, hepatic function tests, renal function tests, electrolyte balance, albumine), and other prognostic factors have been proposed, including tobacco use, alcohol use, the extent of disease (metastatic or localized), Gleason score and response to hormonal therapy. However, the real prognostic value of such factors has not been fully defined [23].

Acute renal failure can be one of the many complications associated with malignancy [24] and the monitoring of urea, uric acid and creatinine levels are important in PCa patients. Similarly, the hepatic function can be altered in PCa and the dosage of hepatic function tests as aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP) and Gamma-glutamyltransferase (GGT) is necessary. Elevated lactate dehydrogenase (LDH) levels are consistently reported as a prognostic factor for poor survival in PCa [25], and the total serum ALP partly reflects osteoblastic activity, which is likely to be more pronounced in patients with larger volume or aggressive bony metastatic disease [26]. Furthermore, there is some evidence to use GGT as an indicator of cancer risk [27]. On the other hand, the electrolyte imbalance in cancer patients can be induced by various factors. Thus, it is important to verify the ion levels in the serum of PCa patients. Finally, associations between albumin concentrations and mortality have been widely reported in patients with various diseases, including cancer [28].

Recently, the role of cholinesterases was investigated in studies carried out in our laboratory with acute lymphoblastic leukemia [29] and in hypertensive and ischemic patients [30], but information about the activities of these enzymes have been conflicting in patients with PCa. Then, in attempt to investigate the potential role of AChE and BChE in the etiology of PCa, as well as the possible interference of different parameters in the enzyme activities, we examined the influence of Gleason score, bone metastasis and hormonal therapy on plasma BChE and total blood AChE activities, two enzymes involved in biological functions, such as proliferation, and cellular differentiation. Furthermore, we also verified various biochemical (LDH, hepatic function tests, renal function tests, electrolyte balance, albumine), and other prognostic factors (tobacco use, alcohol use, the extent of disease, Gleason score and response to hormonal therapy) in PCa patients.

2. Patients and methods

2.1. Patients

The sample consisted of 66 PCa patients aged 72.43 ± 5.89 years from the Oncology-Hematology Laboratory of the Hospital of the Federal University of Santa Maria. Patients included in this study were diagnosed with PCa based on histological evaluation (positive biopsy results). For purposes of analysis, patients with PCa were further divided into different groups for each of three distinct parameters: metastasis, hormonal therapy with goserelin or cyproterone acetate and Gleason score. Consent was given by family members of all the patients included in this work.

The control group consisted of 40 individuals aged 71.40 ± 3.64 years, who presented normal blood pressure, were free from diabetes mellitus, alcoholism, cigarette smoking, chronic diseases, and had not been submitted to any pharmacological therapy. All subjects gave written informed consent to participate in the study. The protocol was approved by the Human Ethics Committee of the Health Science Center from the Federal University of Santa Maria, protocol number 23081.09047/2008-47. Ten milliliters of blood was obtained from each patient and used for analysis. The same procedure was carried out for the control group. Patient general characteristics are shown in Table 1.

2.2. Chemicals

Acetylthiocholine iodide (ASCh), 5,5′-dithio-bis-2-nitrobenzoic acid (DTNB, Ellman's reagent) and Triton X-100 were obtained from Sigma (Deisenhofen, Germany), ethopropazine hydrochloride from Aldrich (Steinheim, Germany). All the other reagents used in the experiments were of analytical grade and of the highest purity.

2.3. Sample preparation

The blood was collected in vaccuntainer tubes using EDTA as anticoagulant. For AChE activity in whole blood, the samples were hemolized with phosphate buffer 0.1 M, pH 7.4 containing Triton X-100 (0.03%) and stored at −20 °C for 1 week. For BChE activity the plasma was separated and stored at −20 °C to posterior analyses. The blood was collected in vaccutainer tubes without an anticoagulant system and centrifuged at 5000 rpm for 10 minutes. The precipitate was discarded and the serum was used to biochemical determinations.

2.4. Biochemical determinations

A blood sample was obtained and serum was used to the determination of LDH, hepatic function tests, renal function tests, electrolyte balance and albumin. AST, ALT, ALP and GGT were measured for the hepatic function testing. Urea, uric acid and creatinine were used to determine the renal function. All measure-

Table 1
Characteristics of patients.

Variable	Patients
Gleason	< 7 (40%)
	= 7 (37%)
	> 7 (23%)
Age (years)	< 70 (24%)
	70–80 (53%)
	> 80 (23%)
Metastasis	Localized disease = 64%
	Bone metastasis = 36%
Treatment	Not treated = 17%
	Goserelin A. = 68%
	Cyproterone A. = 15%
Family history	Yes = 66%
	No = 34%
Smoker	Yes = 64%
	No = 36%
Alcohol	Yes = 42%
	No = 58%
Occupation	Farmer = 42%
	Others = 58%

ments were performed using standard methods on Cobas MIRA® (Roche Diagnostics, Basel, Switzerland) automated analyzer.

2.5. Whole blood acetylcholinesterase and plasma butyrylcholinesterase activities

Whole blood AChE activity was determined by the method of Elmann et al. [31] modified by Worek et al. [32]. To achieve temperature equilibration and complete reaction of sample matrix sulfhydryl groups with DTNB, the mixture was incubated for 10 minutes prior to addition of substrate. Enzyme activity was corrected for spontaneous hydrolysis of the substrate and DTNB degradation. The butyrylcholinesterase (BChE EC 3.1.1.8) was inhibited by ethopropazine. AChE activity was measured at 436 nm and 37 °C using polystyrene cuvets. The activity of whole blood AChE was calculated from the quotient between AChE activity and protein content and the results are expressed as μmoL/h/mg of protein. The same method was used for the determination of BChE activity in the plasma, except that the acetylcholine substrate was replaced by butyrylthiocholine and the results were expressed in the μmoles BcSCh/h/mg of protein.

2.6. Protein determination

Protein was determined by the Coomassie blue method according to Bradford [33] using bovine serum albumin as standard.

2.7. Statistical analysis

Data are presented as mean ± standard error. The distribution of all dependent variables was examined by the Shapiro-Wilk test and was found not to differ significantly from normal. Data were analyzed statistically by one-way Anova followed by the Duncan's multiple tests. Differences were considered significant when the probability was $P < 0.05$. The SPSS version 13.0 was used for all analyses (SPSS Inc., USA).

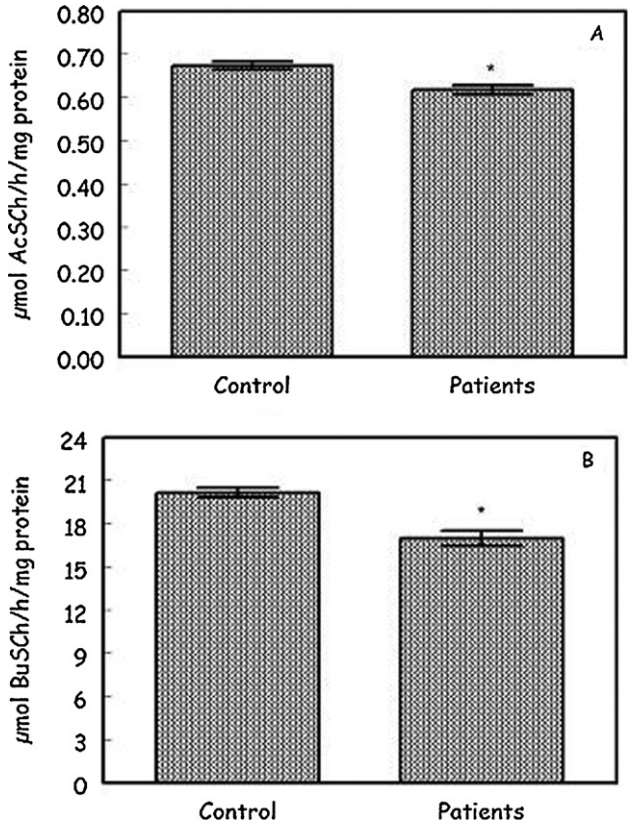

Fig. 1. Acetylcholinesterase (A) and butyrylcholinesterase (B) activities of prostate cancer patients ($n = 66$) and controls ($n = 40$). Each column represents mean ± S.E. Differences are considered significant when $P < 0.05$ (*).

3. Results

3.1. Characteristics of patients

The clinical characteristics of the patient group are shown in Table 1. Most of the patients were classified in the Gleason score less than 7, were between 70 and 80-years-old, had localized disease and were under hormonal therapy with goserelin acetate. Risk factor analysis showed prevalence of smoking and family history of cancer in the patient groups studied. In addition, a great part of PCa patients involved in this study were farmers and reported alcohol use.

3.2. Acetylcholinesterase and butyrylcholinesterase activities

Post-hoc comparisons made by Duncan's test revealed that the AChE in total blood and BChE in the plasma activities were decreased in the PCa patients compared to the control group (Fig. 1A and B).

Fig. 2A and B shows patients divided in groups based on Gleason score. Both AChE and BChE activities were significantly decreased in patients with Gleason score equal and higher than 7 in relation to the other groups.

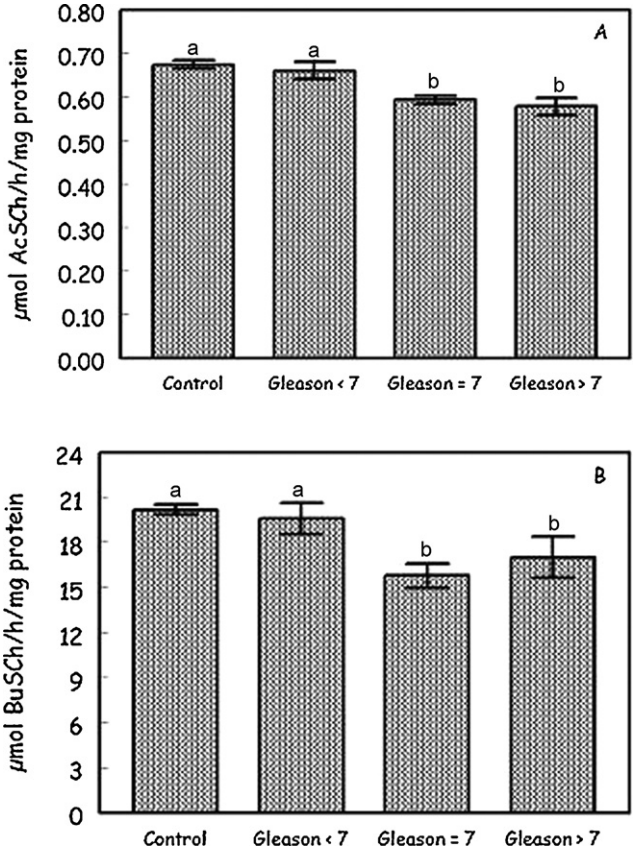

Fig. 2. Acetylcholinesterase (A) and butyrylcholinesterase (B) activities of prostate cancer patients divided by Gleason score. Patients, considering Gleason score, were divided into: Gleason lower than 7 (< 7, $n = 26$), Gleason equal to 7 (= 7, $n = 25$) and Gleason higher than 7 (> 7, $n = 15$). Controls consisted of 40 healthy subjects. Each column represents mean ± S.E. Duncan's multiple range tests: groups that show different letters are statistically different ($P < 0.05$).

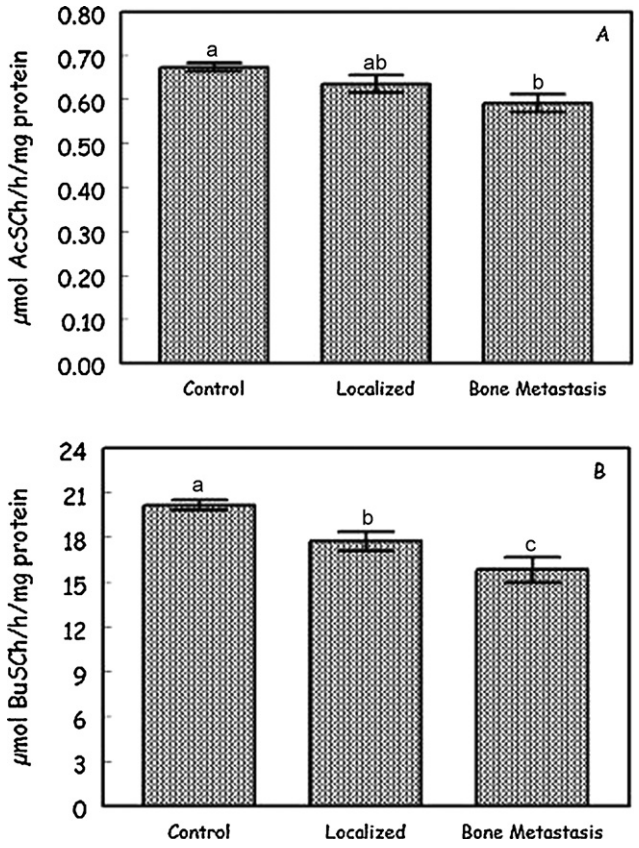

Fig. 3. Acetylcholinesterase (A) and butyrylcholinesterase (B) activities of prostate cancer patients divided by presence or no of metastasis. Patients, considering metastasis, were divided into: localized disease ($n = 42$) and bone metastasis ($n = 24$). Controls consisted of 40 healthy subjects. Each column represents mean ± S.D. Duncan's multiple range tests: groups that show different letters are statistically different ($P < 0.05$).

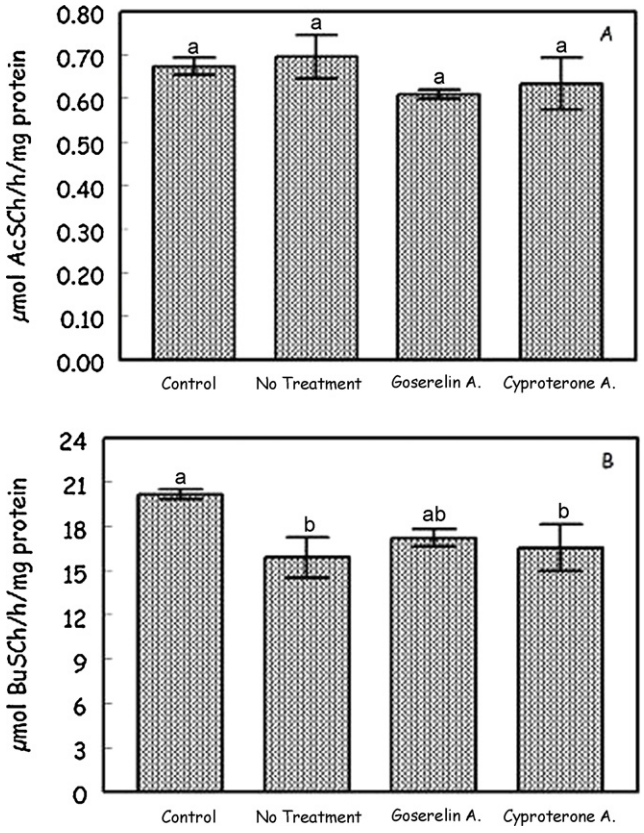

Fig. 4. Acetylcholinesterase (A) and butyrylcholinesterase (B) activities of prostate cancer patients divided by treatment. Patients, considering treatment, were divided into: patients who had not received any therapy preceding the blood sampling (no treatment, $n = 11$), patients undergoing treatment with Goserelin Acetate ($n = 45$) and patients undergoing treatment with Cyproterone Acetate ($n = 10$). Controls consisted of 40 healthy subjects. Each column represents mean ± S.D. Duncan's multiple range tests: groups that show different letters are statistically different ($P < 0.05$).

Fig. 3 shows a comparison of patients with localized PCa and bone metastatic disease with the control group. Post-hoc comparisons made by Duncan's test revealed that the AChE activity (Fig. 3A) was decreased only in patients with bone metastasis in relation to the other groups. Regarding the BChE activity, Fig. 3B shows a reduced activity in all patients in relation to the controls, however, the highest reduction was observed in patients with bone metastasis.

AChE activity in patients divided by treatment is shown in Fig. 4A. No significant difference was observed between groups of patients and controls. On the other hand, post-hoc comparisons made by Duncan's test revealed that the BChE activity was decreased in patients who had not received any therapy or treated with cyproterone acetate when compared to the controls.

3.3. Biochemical determinations

Tables 2 and 3 show the biochemical determinations in patients divided in different groups considering the presence or absence of metastasis, standard treatment (without previous treatment, goserelin acetate or cyproterone acetate) and Gleason score.

Table 2
Biochemical determination (LDH, GGT, ALP, urea, creatinine and uric acid) in prostate cancer patients divided in groups based on type of treatment, Gleason score and bone metastasis.

	LDH (U/L)	GGT (U/L)	ALP (U/L)	Urea (mg/dL)	Creatinine (mg/dL)	Uric Acid (mg/dL)
Control	144.42 ± 3.76	29.15 ± 1.40	88.42 ± 3.31	26.00 ± 1.04	0.88 ± 0.04	4.73 ± 0.14
Type of Treatment						
No treatment	231.33 ± 36.45[a]	49 ± 3.43[a]	259.66 ± 120.23[a]	49.95 ± 12.67[a]	1.03 ± 0.16	5.55 ± 1.05
Goserelin A.	223.69 ± 12.26[a]	39 ± 5.83	150.41 ± 31.28	47.16 ± 2.74[a]	1.43 ± 0.21	5.27 ± 0.24
Cyproterone A.	261.11 ± 27.47[a]	22.2 ± 1.24	88.77 ± 13.45	42.73 ± 5.04[a]	1.02 ± 0.19	4.6 ± 1.54
Gleason Score						
< 7	248 ± 17.66[a]	19.8 ± 1.56	123.43 ± 29.43	43.05 ± 2.41[a]	1.32 ± 0.32	5.3 ± 0.40
= 7	245.43 ± 22.45[a]	36.63 ± 7.3	157.13 ± 53.07	47.51 ± 5.73[a]	1.18 ± 0.23	4.87 ± 0.32
> 7	183.37 ± 21.98[a]	66.5 ± 25.58a	269.25 ± 43.65[a]	50.33 ± 8.59[a]	1.22 ± 0.16	5.37 ± 0.73
Bone Metastasis						
Yes	219.88 ± 15.83[a]	43.23 ± 9.73	211.26 ± 51.18[a]	49.22 ± 4.56[a]	1.51 ± 0.28[a]	4.88 ± 0.30
No	239.86 ± 14.46[a]	35.75 ± 7.76	101.03 ± 18.11	44.63 ± 2.27[a]	1.18 ± 0.98	5.48 ± 0.32

LDH = lactate dehydrogenase; GGT = gamma-glutamyltransferase; ALP = alkaline phosphatase.
[a] A significant difference at $P < 0.05$ from lines not labeled with this letter.

Table 3
Biochemical determination (Na, K, Ca, Mg, AST, ALT and albumin) in prostate cancer patients divided in groups based on type of treatment, Gleason score and bone metastasis.

	Na (mEq/L)	K (mEq/L)	Ca (mg/dL)	Mg (mg/dL)	AST (U/L)	ALT (U/L)	Albumin (g/100 mL)
Control	140.95 ± 0.51	4.59 ± 0.05	9.44 ± 0.06	2.05 ± 0.02	23.55 ± 0.78	22.80 ± 1.09	4.12 ± 0.06
Type of Treatment							
No treatment	139.66 ± 1.08	4.46 ± 0.16	9.11 ± 0.23	1.90 ± 0.1	55.43 ± 2.4[a]	37.5 ± 1.5[a]	4.67 ± 0.04
Goserelin A.	138.74 ± 0.61	4.39 ± 0.06	9.16 ± 0.09	2.13 ± 0.03	24.48 ± 4.4	22.61 ± 1.88	4.11 ± 0.11
Cyproterone A.	139.12 ± 1.80	4.51 ± 0.23	9.21 ± 0.11	1.97 ± 0.12	23.4 ± 4.3	23.8 ± 3.77	4.16 ± 0.28
Gleason Score							
< 7	139.05 ± 1.19	4.49 ± 0.12	9.14 ± 0.52	2.08 ± 0.05	20.6 ± 2.55	20.4 ± 2.07	4.22 ± 0.13
= 7	138.60 ± 0.56	4.42 ± 0.11	9.10 ± 0.12	2.11 ± 0.07	21.14 ± 1.79	24.71 ± 2.31	4.04 ± 0.17
> 7	137.77 ± 3.23[a]	4.40 ± 0.15	9.25 ± 0.26	2.11 ± 0.09	28.00 ± 2.78	50.32 ± 4.72	4.02 ± 0.41
Bone Metastasis							
Yes	138.53 ± 0.58[a]	4.38 ± 0.08	9.14 ± 0.12[a]	2.09 ± 0.04	30.22 ± 4.91	21.55 ± 2.36	3.95 ± 0.15
No	139.24 ± 0.88	4.45 ± 0.09	9.18 ± 0.10	2.11 ± 0.05	22.10 ± 1.81	25.35 ± 2.38	4.27 ± 0.10

AST = aspartate aminotransferase; ALT = alanine aminotransferase.
[a] A significant difference at $P < 0.05$ from lines not labeled with this letter.

Post-hoc comparisons made by Duncan's test revealed that DHL activity and levels of urea in the serum were increased in all PCa patients. Our results show that ALP activity was elevated only in patients that had not received any therapy preceding the blood sampling, with Gleason score higher than 7 and in patients with bone metastasis compared with other groups. In relation to the GGT activity, our results show elevated activity in patients that had not received any therapy and in patients with Gleason score higher than 7. The activities of ALT and AST were increased in patients that had not received any therapy. Creatinine level was increased only in patients with bone metastasis. On the other hand, calcium level was decreased in these patients. Levels of sodium were decreased in patients with Gleason score higher than 7 and with bone metastasis. Nevertheless, for the uric acid, potassium, magnesium and albumin, there was no significant difference between the groups.

4. Discussion and conclusion

Prostate cancer is the sixth most common type of cancer worldwide and it is a considerable health risk for men throughout the world. It has been proposed that there may be a hereditary component to PCa risk, since family history of PCa is a well-established risk factor for PCa risk in men [34]. In accordance, our study demonstrated an increased PCa risk for men with a family history of any cancer or PCa. In our study, we observed that most PCa patients were current smokers. One important relationship between tobacco smoking and cancer is well established [35]. Cigarette smoke contains hundreds of carcinogenic substances that have demonstrable effects on all phases of cancer development. Tumor initiation, promotion and progression have been associated with compounds found in tobacco smoke in a variety of experimental tumor model systems [36]. Moreover, a significant number of PCa patients were farmers and reported alcohol consumption. According to Parent et al. [10], farmers exposed to high levels of pesticides had a two-fold excess risk of PCa compared to unexposed farmers. Moreover, alcohol consumption has been shown to alter sex steroid metabolism and thus could theoretically play a role in PCa development [37].

AChE is an essential enzyme in the nervous system that plays a key role in terminating neurotransmission at cholinergic synapses. AChE is a constituent of various cell types and tissues that include nervous tissues, human fibroblasts, rat kidney cells, human erythrocytes and human megakaryocytes [38,39]. In these tissues, the biological role of AChE is not limited to its classical role in hydrolyzing the neurotransmitter acetylcholine, but includes non-classical roles, such as cellular proliferation and differentiation, suggesting a possible influence of cholinestases in tumorogenesis.

Our results show that the AChE and BChE activities were decreased in PCa patients in relation to the control group. These results support the hypothesis that the alteration in cholinesterase activity in tumors may arise from an increased degradation or release of these enzymes. Another important aspect to be discussed is that a decrease in the cholinesterase would affect mainly the hydrolysis of acetylcholine. According to Song et al. [40], this chemical compound stimulates cancerous cells growing in lung tumors. The drop in cholinesterase activity and the consequent increased amount of acetylcholine could lead to a cholinergic overstimulation and increase the cell proliferation in cancer. In the context of cancer, the opposite variation of AChE and BChE activities in human breast carcinoma [41], the decrease of AChE activity in metastatic lymph nodes [42], the aggressiveness of human astrocytoma linked to changes in the composition of AChE variants [43], the correlation between the high levels of cytoplasmic AChE with decreased survival in ovarian cancer patients [44] and the function of cholinesterases in the male reproductive physiology [45] are worth mentioning.

When the patients were divided in groups based on clinico-pathological characteristics interesting results were observed. AChE and BChE activities were modulated differently in relation to the Gleason score, presence or absence of metastasis and use of hormonal therapy. This may indicate that the cholinesterase activities are being affected differently by these conditions. Interestingly, we have observed a decrease in cholinesterase activities in the cancer group with a Gleason score greater than 7. Furthermore, these findings indicate that advanced PCa is associated with a decreased cholinesterase activity and consequently high acetylcholine concentration.

When the patients were divided considering the presence or absence of the metastasis, a reduction in the AChE activity only in patients with metastasis was observed. In relation to the BChE activity the major decrease was observed in patients with bone metastasis as well. These results are interesting and support the idea that acetylcholine may be involved in the process of metastasis. Both cholinesterases have been implicated in the development processes as a cellular proliferation stimulator [46,47]. AChE can be considered a marker of early differentiation [48], while BChE may be involved in cellular migration and fiber guidance [49].

On the other hand, there was no change in AChE activity when considered the treatment type. Patients who did not receive any previous treatment or in treatment with cyproterone presented BChE activity decreased. Furthermore, it is possible to suppose that the change of BChE activities in tumor is a consequence of the neoplastic transformations and that it contributes to the maintenance of the tumorigenic process. However, in order to explain

these modifications in the BChE activity in different treatment, further investigation is required, since is the first time that cholinesterase activities were determined based on treatment type in PCa patients.

In relation to biochemical determinations in PCa patients, several changes were verified. LDH activity and levels of urea in the serum were increased in all PCa patients. The prognostic role of LDH has been widely investigated in special cancer groups [50]. Elevated LDH is consistently reported as a prognostic factor for poor survival in lung cancer, pancreatic cancer and PCa [25]. Regarding the renal damage represented by increased urea level, it is difficult to quantify the extent of renal complications associated with malignancy, as renal dysfunction can be present before the identification of malignancy, coincide with the diagnosis of malignancy, or be a secondary or tertiary effect of treatment [24].

Our results show that ALP activity were elevated only in patients that had not received any therapy preceding the blood sampling, with Gleason score higher than 7 and in patients with bone metastasis when compared with other groups. Total serum ALP is a commonly and serially measured marker that is inexpensive and readily available. ALP partly reflects osteoblastic activity, which is likely to be more pronounced in patients with larger volume or aggressive bony metastatic disease [26]. In relation to the GGT activity, our results show an elevated activity in patients that had not received any therapy and in patients with Gleason score higher than 7. Our results are in accordance with Hemelrijck et al. [51] that show a positive association between GGT levels and tumor incidence that may be explained by the link between GGT and the cell redox state. The activities of AST and ALT were increased in patients that had not received any therapy. The liver enzymes ALT and AST are biomarkers known to be specific for liver damage as they mainly appear in the liver and their levels increase when there is injury to the liver. Thus, an increase in these enzyme activities indicates a liver damage in patients that had not received any therapy.

In addition, creatinine level was increased only in patients with bone metastasis. Therefore, a marked increase in serum creatinine confirms an indication of functional damage to the kidney in this group of patients. On the other hand, calcium level was decreased in these patients. Tandon and Rizvi reported that hypocalcemia can be a manifestation of PCa metastatic to bone [52]. Levels of sodium were decreased in patients with Gleason score higher than 7 and with bone metastasis. Hyponatremia is often observed in patients with breast cancer, renal cancer, prostate cancer, and paraneoplastic syndrome. According to Shibata [53], one of the causes of hyponatremia is antidiuretic hormone-producing tumor.

The medical literature shows several examples of an inverse relationship between serum albumin levels and survival in patients with advanced cancer [28]. However, in our study no significant difference was observed in the albumin levels between the PCa and controls. Although the breakdown of cells, observed in some patients with cancer, may increases the blood levels of uric acid, magnesium and potassium, in our study there were no changes in these parameters in patients with PCa.

Finally, our study indicates that biochemical prognostic factors, like lactate dehydrogenase, hepatic function tests, renal function tests and electrolyte balance are altered in PCa patients. In addition, our results could show a possible relationship between the inhibition of cholinesterase activities and cellular proliferation in PCa, indicating that these enzymes may be functionally important in neoplastic cell transformation. All the clinical and pathological characteristics are fundamental to the PCa prognosis, and our findings show alterations in the cholinesterase activities and in the biochemical determinations considering such characteristics like the presence of metastasis, standard treatment used and Gleason score. Therefore, the role of the non-neuronal cholinergic system in different diseases (including PCa) needs to be clarified in more detail in order to optimize a future targeted-therapy.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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