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Serum levels of interleukin-2 differ between prostate cancer and benign prostatic hyperplasia

Níveis séricos de interleucina-2 diferem entre câncer de próstata e hiperplasia benigna da próstata

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ABSTRACT

Objective: Investigation onthe systemic inflammatory profile ofpatients affected by prostate cancer (PCa) or prostatic hyperplasia (BPH) may contribute to characterize the pathological profile as well as enable identification of markers and promote alternatives for appropriate, less invasive treatments.

Methods: This research compared serum levels of 10 classic inflammatory mediators among patients aged 50 years or older affected by PCa or BPH. For this, clinical, biochemical, metabolic, anthropometric and inflammatory aspects of each patient was considered.

Results: From the statistical analysis, a weakpositive correlation (r = 0.16) between IL-2 with serum total PSA values was found. In addition, median serum IL-2 values were three times higher in patients with PCa compared to BPH patients.

Conclusion: By interpretation of current literature, we hypothesize that the activity of infiltratedtype M1 macrophages and activated cytotoxic cells in the neoplasm milieu might explain this increase of IL-2 as part of anendogenous anti-neoplastic response.

Key words: interleukins; cytokines; inflammation; prostate; neoplasms; prostatic hyperplasia, aging.

RESUMO

Objetivo: *A investigação do perfil inflamatório sistêmico de pacientes acometidos por câncer de próstata (CaP) ou hiperplasia prostática (HPB) pode contribuir para caracterizar o perfil patológico, bem como permitir a identificação de marcadores e promover alternativas de tratamentos adequados e menos invasivos.*

Métodos: *Esta pesquisa comparou os níveis séricos de 10 mediadores inflamatórios clássicos em pacientes com 50 anos ou mais afetados por CaP ou HPB. Para tanto, foram considerados os aspectos clínicos, bioquímicos, metabólicos, antropométricos e inflamatórios de cada paciente.*

Resultados: *A partir da análise estatística, foi encontrada uma correlação positiva fraca (r = 0,16) entre a IL-2 com os valores séricos de PSA total. Além disso, os valores medianos de IL-2 no soro foram três vezes maiores em pacientes com CaP em comparação com pacientes com HPB.*

Conclusão: *Pela interpretação da literatura atual, hipotetizamos que a atividade de macrófagos do tipo M1 infiltrados e células citotóxicas ativadas no meio da neoplasia pode explicar esse aumento de IL-2 como parte da resposta antineoplásica anendógena.*

Palavras-chave: *interleucinas; citocinas; inflamação; próstata; neoplasias; hiperplasia prostática, envelhecimento.*

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INTRODUCTION

Benign prostatic hyperplasia (BPH) and prostate cancer (PCa) are the most common chronic urological conditions in the male population after the age of 50[1,2]. There are reports that about 50% of men have BPH at the 6th decade of life, with a frequency that rises to 90% in the 9th decade[3]. As the second leading cause of death by cancer among American men, six out of ten diagnoses performed for PCa occur at the age of 65 years or older[1]. In this line, the Brazilian scenario points out that PCa corresponds to the most frequent non-melanoma cancer among men, and highly associated with aging[4].

BPH occurs when stromal and epithelial cells of the prostate in the periurethral region proliferate from replicative conditions influenced by inflammation and, resulting in gland hyperplasia and consequent obstruction of the urinary canal that triggers typical symptoms. Prostatic inflammation is strongly related to the pathogenesis of BPH, being supported by epidemiological, histopathological and molecular evidence[5,6]. However, there is no evidence that BPH is responsible for the development of PCa[2].

Concerning contributors to the development of PCa, family inheritance appears as the main risk factor for the disease, alongside ethnic group (population ancestry) and lifestyle habits as additional factors[7,8]. Prostate tissues affected by tumor express high levels of different inflammatory mediators with the potential to produce systemic consequences[9]. Among numerous characteristics, the ability to promote chronic inflammation usually corresponds to an important peculiarity of cancer, being estimated that 20% of allcancer cases among adults are associated with tissue inflammation of either focal or diffuse nature[10]. Accumulated chemotactic factors can enable neoplastic evasion through blood and lymphatic circulation, with chronic inflammation associated with poor prognosis[11].

The microenvironment affected by cancer has different cell types and cytokines. Factors such as IL-6 and CSF-1 derived from neoplastic cells drive myeloid precursors to differentiation into macrophages[12]. In addition, studies have suggested that interleukin (IL)-6 cooperates with the signaling of growth factors in the prostate microenvironment to promote tumorigenesis and the progression of malignancy[13]. Cytokines such as TGF-β and IL-1, for example, have already been described in prostate tissue as possible prognostic biomarkers of PCa[14].

As an alternative for monitoring different prostatic conditions, the measurement of the prostate-specific antigen (PSA) is currently recommended by most urological medical societies worldwide, using a reference value of 4 ng / mL in screening procedures for early detection of PCa. Despite the clinical utility as an organ-specific marker, PSA dosages are susceptible to alteration in different prostatic conditions (prostatitis, benign hyperplasia, and cancer, for example), and its clinical use is recommended to in association with different procedures to increase the diagnostic specificity[15].

Therefore, to assess of a differentiated systemic inflammatory profile among patients affected by highly prevalent prostatic diseases (such as CaP and BPH) may be an effective strategy to yield a precise distinction between these pathologies, as well as helping to understand their development, prognosis, and alternatives for more appropriate and less invasive treatments.

Bearing in mind the scarcity of precise diagnostic methods for similar pathologies and the intrinsic role of inflammatory mediators in carcinogenic processes, our research is dedicated to the investigation of possible biomarkers that make the distinction between BPH and PCafeasible[16]. For this, the present study compared the serum levels of a set of 10 classic inflammatory mediators between patients affected by PCaor BPH.

MATERIAL AND METHODS

A cross-sectional study that analyzed male patients aged 50 years or older consecutively admitted from August 2017 to July 2018 at the Urology Outpatient Service of University Hospital of Brasília. Each individual was submitted to a clinical protocol focused on the characterization of prostatic alteration (PCa or BPH) if any.In parallel to the urological evaluation, clinical, biochemical, metabolic, anthropometric and inflammatory aspects of each patient were analyzed.

Urological Evaluation: Procedures involved a comprehensive clinical investigation of classic signs and symptoms of physiological changes in the excretory and reproductive systems of patients[17], such as reduced urinary jet or voiding effort, a sensation of incomplete bladder emptying or intermittency, dysuria, nocturia, and hematospermia. Then, the total and free PSA levels were evaluated, followed by an analysis of the prostatic condition of each patient by means of digital rectal examination, with assessment of consistency (fibroelastic, hardened or with nodules), surface (smooth or irregular), contours (sharp or inaccurate) and volume (normal or increased), as well as the presence or absence of the median groove. Patients with prostatic nodules detected by digital rectal examination and/or with high PSA levels (> 4.0 ng / mL) were referred for biopsy, with or without the described signs and symptoms.

Patients with biopsy results indicative of acinar

adenocarcinoma and who had not undergone a previous radical prostatectomy procedure comprised the study's PCa group, with the Gleason Score determined for each.

Upon admission to the study, peripheral blood drawn to yield serum to allowthe laboratoryanalyses for the present study, with a portion of biological samples frozen at -80ºC for analysis of the inflammatory panel.

Laboratory Analysis: Clinical and Biochemical Tests: The biological samples collected were processed following protocols and routine laboratory analytical technical instructions. The glycemic, lipemic, enzymatic, metabolic and inflammatory profiles of each patient were analyzed.

The fasting levels of glucose, total cholesterol, triglycerides and HDL were carried out through colorimetric tests, using the InVitro® Human Star 600 equipment as automation.Through the turbidimetry analytical technique, the ultrasensitive PCR values were obtained. With the help of bromocresol green indicator dyes and Biuret reagent, the levels of albumin and total proteins, respectively, were determined.The values of TGO (AST) and TGP (ALT) were analyzed using the Reitman-Frankel automation technique. The estimates of the glomerular filtration rate were obtained using the Cockcroft-Gault formula. Through the colorimetric test with alkaline picrate reagent, creatinine values were determined. LDL levels were obtained according to Friedewald 's formula, and finally, VLDL - c, was obtained by calculating VLDL = TG / 5, where TG corresponds to triglycerides.

The complete blood count was performed using the automated hematological system CELL-DYN Ruby®. Glycated hemoglobin was obtained using high-performance liquid chromatography (HPLC), while levels of insulin, vitamin D, homocysteine, TSH, free T4 and total and free PSA were obtained by electrochemiluminescence using the Cobas E411 system from the brand Roche®.

Inflammatory Panel: On the occasion of the biochemical evaluations, whole blood was drawn and the serum obtained was kept frozen at -80 °C until thawed for the assessment of the immune mediators. Cytokine concentrations were assessed by a multiplexed flow cytometry method using two sets of bead-based immunoassays known as the Human Th1/Th2 II kit and the Human Inflammatory kit manufactured by BD Biosciences® (San Diego, CA, USA), used according to the manufacturer protocols and which all together yielded measurements for 9 different circulating mediators, as follows: interferon-γ (IFNγ), interleukin-1β (IL1β), IL2, IL4, IL6, IL8, IL10, IL12.p70, tumor necrosis factor- α (TNFα) and C-reactive protein.

Briefly, the lyophilized cytokine standards and the serum samples were processed and the results acquired using the BD FACSVerse® flow cytometer, FL4 channel. Three hundred events were acquired for each cytokine bead used. Data were analyzed using the FCAP software, version 3.0 (BD Biosciencesâ, San Diego, CA, USA). Standard curves for each cytokine were generated using a standard mixture of mediators supplied. The concentration in each serum was determined by interpolation from the corresponding standard curve. Whenever a given cytokine was assessed by both kits, the mean value obtained was considered.

The C-reactive protein was assessed using the CRP Human Instant ELISA™ Kit, manufactured by Invitrogen (Thermo Fisher Scientific, Waltham, MA USA).

Statistical Analyses: To address the aim of evaluating the occurrence of an association between baseline, clinical characteristics of the sample with the condition under investigation, our statistical analyses were initiated by comparing anthropometric and biochemical traits of potential confounding effects in the main model. The normal distribution of all variables was assessed using the Kolmogorov-Smirnov test. Then, a comparison of levels of immune mediators across carries of prostate cancer and BPH was carried out. The Student's *t-test* and the Mann-Whitney test were used for comparison of central tendency scores of parametric and non-parametric data, respectively, with data expressed as mean ± standard deviation or median with interquartile intervals, accordingly. The association between continuous traits was evaluated using Pearson's correlation test. For all analyses, a $P < 0.05$ was rendered as a threshold of statistical significance. All analyses were performed with the Statistical Package for the Social Sciences (SPSS) for Windows (version 17.0).

RESULTS

After medical diagnostic procedures, a total of 182 patients with an average age of 66 years were identified as having CaP or BPH. Recognized as one of the most frequent prostatic disorders among long-lived men, BPH corresponded to the highest proportion (n = 162; 89%) of patients with gland dysfunction in this study when compared to those with CaP (Table 1). The clinical and biochemical characteristics observed in the patients demonstrated a high prevalence of metabolic disorders regardless of the prostate condition, which is illustrated by the average values for lipemic and glycemic indexes at a borderline or supraphysiological level.

Levels of total and free PSA proved to be consistently high among PCa patients when compared to BPH (Table 1). Since in PCa, PSA is mostly complexed with α-1-chymotrypsin and α-2-macroglobulin, the indices of the ratio of free PSA / total PSA, as expected, were higher in patients with BPH (Table 1).

TABLE 1 - Clinical and biochemical serum characteristics of the individuals according to the diagnosis of prostate cancer (PCa) or benign prostatic hyperplasia (BPH)

	PCa (n = 20)	BPH (n = 162)	P*
Age, years	66.0 ± 11.5	67.5 ± 10.1	0.533
Body mass index, kg/m^2	26.2 ± 3.8	25.7 ± 4.3	0.646
Glucose, mg/dl	104.3 ± 24.2	101.4 ± 32.4	0.696
HbA1c, %	5.8 ± 1.1	5.8 ± 1.3	0.985
Insulin, mU/mL	7.8 [3.2; 9.2]	5.7 [2.8; 10.1]	0.483†
HOMA index	1.8 [0.8; 2.3]	1.4 [0.6; 2.5]	0.414†
Triglyceride, mg/dL	141.9 ± 42.1	155.9 ± 115.2	0.286
Total cholesterol, mg/dL	204.2 ± 37.2	195.4 ± 47.5	0.424
VLDL cholesterol, mg/dL	28.4 ± 8.4	28.8 ± 16.2	0.857
LDL cholesterol, mg/dL	126.5 ± 35.2	112.4 ± 42.7	0.158
HDL cholesterol, mg/dL	49.4 ± 10.8	50.9 ± 12.9	0.626
SGOT, U/L	27.3 ± 11.7	27.4 ± 12.2	0.985
SGPT, U/L	25.6 ± 17.1	26.0 ± 14.7	0.911
γGT, U/L	56.0 ± 42.6	53.0 ± 44.0	0.874
Creatinin, mg/dL	1.0 ± 0.2	1.1 ± 0.3	0.505
Total protein, g/dL	7.2 ± 0.5	7.4 ± 0.4	0.196
Albumin, g/dL	4.2 ± 0.4	4.4 ± 0.4	0.221
25-Hydroxy D3, nmol/L	29.4 ± 10.2	31.5 ± 12.8	0.485
CRP, mg/L	1.12 ± 0.77	1.10 ± 0.68	0.949
TSH, mU/L	1.8 [1.0; 3.2]	1.9 [1.2; 3.0]	0.901†
Total PSA, ng/mL	21.8 [10.5; 34.6]	2.4 [1.1; 5.2]	<0.001†
Free PSA, ng/mL	1.8 [0.5; 4.3]	0.4 [0.2; 0.8]	<0.001†
Free/Total PSA ratio, %	8.0 [5.4; 16.1]	19.7 [13.0; 26.0]	<0.001†

CRP: C-reative protein; HbA1c: glycatedhemoglobin type-A1c; HOMA: homeostasis model assessment; HDL: high densitylipoprotein; LDL: low density lipoprotein; VLDL: very low density lipoprotein; SGOT: serumglutamic-oxaloacetic transaminase; SGPT: serumglutamic-pyruvic transaminase; γGT: gamma-glutamyl transferase; TSH: thyroid stimulating hormone; PSA: Prostate-specific antigen. Data expressed within each group as mean ± standard deviation or median with interquartile intervals in brackets. *P values for comparison of differences using the Student'st test, exception for use of the Mann-Whitney test† for non-parametric data.

In the health conditions presented, an exploratory analysis of the correlation between PSA levels (free, total and ratio) and the levels of inflammatory mediators found a weak positive correlation (r = 0.16) between IL-2 (but not of other cytokines) with total serum PSA values (Table 2). A similar trend was observed with free PSA scores.

Regarding prostatic conditions observed by digital rectal examination in patients with BPH, 18% (n = 29) showed changes on what concerns consistency. However, for patients with PCa, this examination demonstrated prostatic alteration perceptible to touch in most patients (n = 19; 95%), with the presence of nodules and induration being the most frequent phenotypes (60% of cases of PCa). The Gleason score was determined for patients with PCa, with the most frequent score (n = 8; 40%) being that of intermediate grade 3 + 4, with those of low grade 3 + 3 corresponding to 30% (n = 6) and those at high risk (Gleason ≥ 8) represented 30% (n = 6) of the total analysed.

When comparing the circulating levels of immunological mediators according to the diagnosis of PCa or BPH, serum IL-2 values were shown to be three times higher in median terms among patients with PCacompared to patients with BPH (Table 3), with no other cytokine levels varying across groups.

DISCUSSION

Neoplastic and non-neoplastic cells are influenced by the inflammatory process that controls, delineates and remodels prostate tissue. In response to tissue damage, inflammation is driven by a dynamic mechanism of production of growth factors, cell-matrix remodelling enzymes, and cytokines, aiming at tissue repair[12].

One study evaluated levels of inflammatory mediators in the seminal plasma of oligozoospermic men and detected IL-2, suggesting the prostate as the source of this cytokine, at least under a physiologically adverse condition[18]. Another study compared the in situ expression of inflammatory mediators in different prostate diseases and found higher levels of IL-2 in cases of PCa when compared to BPH[19]. As PSA represents an organ-specific antigen, prostatic alterations due to inflammation, hyperplasia or neoplasia that culminate in cell lysis would justify the increase in IL-2 associated with total PSA, in line with the result found herein.

In this context, inflammatory infiltrates in human prostates

TABLE 2 - Correlation analyses of raw serum forms of the prostate-specific antigen (total and free) and their ratio across levels of the inflammatory mediators investigated in the162 older men at admission

	IFNγ	IL1β	IL2	IL4	IL6	IL8	IL10	IL12	TNF
Total PSA, ng/mL	0.03; 0.740	-0.01; 0.894	0.16; 0.034#	0.05; 0.554	0.02; 0.850	0.02; 0.790	0.02; 0.781	0.04; 0.595	0.04; 0.587
Free PSA, ng/mL	0.03; 0.678	0.00; 0.989	0.13; 0.086	0.04; 0.660	0.00; 0.977	-0.01; 0.901	0.00; 0.987	0.02; 0.810	0.02; 0.752
Free/Total PSA ratio	0.05; 0.509	-0.02; 0.790	0.10; 0.217	0.10; 0.181	-0.02; 0.802	-0.04; 0.671	0.03; 0.734	0.09; 0.264	0.08; 0.301

The Pearson's correlation test was used. Data are expressed in correlation index and significance level (two digitr; three digit P). CRP: C-reative protein; INF: interferon; IL: interleukin. Significance threshold set at P ≤ 0.05. Superscript # represents effect size (d) = 0.16.

TABLE 3 - Circulating levels of immune mediators according to the diagnosis of prostate cancer (PCa) or benign prostatic hyperplasia (BPH)

INF:	PCa (n = 20)	BPH (n = 162)	P*
IFNγ, pg/mL	2.3 [0.7; 3.5]	2.1 [0.7; 3.3]	0.857
IL1β, pg/mL	1.3 [0.3; 2.0]	1.0 [0.0; 2.1]	0.496
IL2, pg/mL	3.0 [0.0; 3.9]	0.0 [0.0; 3.3]	0.034
IL4, pgmL	2.7 [0.5; 4.1]	1.2 [0.4; 3.4]	0.213
IL6, pg/mL	5.0 [2.9; 11.4]	4.1 [2.4; 6.6]	0.355
IL8, pg/mL	14.7 [10.7; 35.0]	17.9 [10.4; 42.6]	0.810
IL10, pg/mL	1.9 [0.1; 2.3]	1.7 [0.0; 2.2]	0.356
IL12, pg/mL	2.0 [0.8; 2.4]	1.3 [0.2; 2.3]	0.122
TNFα, pg/mL	2.3 [0.7; 2.9]	1.5 [0.4; 2.2]	0.286

interferon; IL: interleukin. Data expressed within each group as median with interquartile intervals in brackets. *P values for comparison of differences using the Mann-Whitney test.

are described in the literature and, although their origin is still uncertain, they can be seen in benign and malignant lesions[20], with tumor-associated macrophages (TAMs) abundant in inflammatory infiltrates. Neoplastic tissues[12]. An important dual role of TAMs is observed in neoplasms because they can both have a cytotoxic effect on neoplastic cells (mediated by IL-2, IL12 or IFN) as well as being responsible for the production of growth factors and proteases that contribute to tumor progression[12].

During investigations for the treatment of PCa, IL-2 was found as an important component in the immune response since, from a pro-inflammatory point of view, M1 macrophages release IL-2 to trigger an anti-tumour response[21,22]. While type M2 macrophages mediate an anti-inflammatory response that usually leads to tumour progression, M1 macrophages appear to be able to produce and respond to IL-2[23]. Furthermore, IL2 directly promotes the differentiation of TCD8+ lymphocytes[24], promoting selective targeting for the destruction of tumour cells. Dolman et al demonstrated that infusion of IL-2 suppresses the growth and spread of human prostate carcinoma in severely immunosuppressed mice[25], with probable involvement of TAMs in the response promoted by the mediator. The availability of IL-2 also suggests absence of regulatory T cells (Tregs CD25+ Fox3p+) which are responsible for capturing/neutralizing circulating IL-2, and promoting worse prognosis of PCa[10].

In line with potential benefits from endogenous IL-2 production, therapeutic proposals currently employ IL-2 in effective immunotherapy against human cancers[26]. Long-lasting and complete regressions of metastatic diseases for melanoma and kidney cancer were observed using IL-2 infusions[27]. In addition, in vitro and in vivo experimental models demonstrated that monoclonal antibodyconjugated with IL2 stimulates lymphocyte-mediated antitumor cytotoxicity[28].

Although the design of the present study does not allow the establishment of a cause and effect relationship and has limitations due to the lack of quantification and typing of macrophages present in the prostate gland, the study serves as the basis for experimental approachs investigating novel immunotherapies, especially those using IL-2 and/or stimulated M1 macrophages to demonstrate whether these activation(s) are associated with cancer confinement to the organ and better prognosis.

Therefore, from our results, we suggest that the elevation of circulating levels of IL-2 observed herein could be attributable to an endogenous defence mechanism against the prostate cancer, orchestrated by the activity of M1 macrophages and cytotoxic cells activated, based on the assumption that tumor progression depends on the conditions of the micro environment. However, a possible eligibility of IL-2 as novel biomarker for PCa depends on further studies that should explore the sensitivity and specificity of this marker in a comprehensive clinical context.

Conflicts of Interests: The authors declare they have no competing interests.

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Author contributions: WKE-C was responsible for clinical biochemistry quantifications. GGA assessed the immunological mediators, ACT-F advised on technical procedures and performed quality control assessments. DIVP assisted on statistical analyses. CFM performed the medical assessments. OTN and CFM designed and coordinated the study. OTN, WKE-C and GGA conducted to the writing process, with the two-former responsible for the final version for publication.

Disclaimer: The authors declare minor self-plagiarism by reusing elements from published work of our own to help describing the sample and methods, being provided appropriate reference.

Data availability statement: Data can be made available upon reasonable request to the corresponding author.

Ethical Approval: All procedures with human participants were in accordance to national ethical standards as well as to institutional Ethics Committee on Research (University of Brasília) and with the 1964 Helsinki Declaration and later amendments.

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