Cytokine 63 (2013) 130–134

Contents lists available at SciVerse ScienceDirect

Cytokine

journal homepage: www.journals.elsevier.com/cytokine

Significance of obesity markers and adipocytokines in high grade and high stage prostate cancer in North Indian men – A cross-sectional study

Reshu Tewari [a,b,*], Singh Rajender [c,*], S.M. Natu [a], Apul Goel [d], Divakar Dalela [d], M.M. Goel [a], Pushpa Tondon [a]

[a] Department of Pathology, King Geogre Medical University, Lucknow, India
[b] Department of Gastroenterology and Hepatology, Moti Lal Nehru Medical College (MLNMC), Allahabad, India
[c] Division of Endocrinology, CSIR-Central Drug Research Institute, Lucknow, India
[d] Department of Urology, King Geogre Medical University, Lucknow, India

ARTICLE INFO

Article history:
Received 26 November 2012
Received in revised form 15 March 2013
Accepted 8 April 2013
Available online 10 May 2013

Keywords:
Cytokines
Obesity
Prostate cancer
Benign prostatic hyperplasia

ABSTRACT

Background: Prostate cancer (CaP) in India is the 10th most common malignancy affecting men. CaP incidence in India is low, but rising like other countries. The reasons for this racial disparity are uncertain. The foremost reasons that may underlie regional/ethnic differences are genetic polymorphisms, altered hormonal status, socioeconomic status, and obesity. This study aimed at investigating the role of adipocytokines in stimulating the promotion and progression of CaP.

Methods: A cross-sectional study on histopathologically proven prostate cancer ($N = 95$) and benign prostatic hyperplasia ($N = 95$) patients was undertaken. CaP patients were classified into high-grade ($N = 62$) and low-grade ($N = 33$), and high stage ($N = 31$) and low stage ($N = 64$) groups. The level of body mass index (BMI), waste to hip ratio (WHR), interleukin-6 (IL-6), leptin, and adiponectin were compared between BPH and CaP groups and between grades and stages of prostate cancer.

Results: The level of BMI was significantly ($p < 0.001$) higher in CaP patients (26.58 ± 4.76) in comparison to BPH (22.15 ± 2.90). Similarly, WHR was significantly ($p < 0.0001$) higher in the CaP patients (1.08 ± 0.37) in comparison to BPH (0.86 ± 0.15). Leptin (BPH: 25.60, CaP: 56.00) and II-6 levels (BPH: 9.90, CaP: 32.30) were significantly higher, but adiponectin was significantly lower in CaP patients as compared to BPH. High grade CaP patients had significantly higher BMI and WHR in comparison to low grade, and WHR was also higher in high stage CaP. Leptin and IL-6 level were higher in high stage and high grade, but adiponectin was low in high stage and high grade groups in comparison to low stage and low grade groups.

Conclusions: Higher BMI and WHR correlate with prostate cancer independently, suggesting obesity to be a promoter of poor prostate health. Leptin and IL-6 appear to have stimulating effect on prostate cancer cells inducing the promotion and progression of CaP, but adiponectin appears to be protective against prostate cancer.

1. Introduction

International Agency for Cancer Research (IARC) suggests low incidence of prostate cancer in East Asian countries in comparison to the western countries [1,2]. Prostate cancer in India is the 10th most common malignancy affecting men, though its incidence is rising in India as well [3]. The reasons for this racial disparity are uncertain. The foremost reasons that may underlie these regional/ethnic differences are genetic polymorphisms [4], altered hormonal status [5], socioeconomic status [6], and obesity [7]. Recent studies have suggested metabolic syndrome, including disturbed glucose metabolism and insulin levels, to affect prostate cancer risk [8,9]. BPH is very common among aging men and can cause lower urinary tract symptoms (LUTSs), which can be bothersome and affect the quality of life [10,11]. However, the morbidity due to BPH is of lower grade and the mortality rate is almost nil.

Adipocytes are the major constituents of white adipose tissue, which synthesize and secrete a range of bioactive molecules termed, adipokines [12]. Adipokines released by the adipose cells have been linked with a number of carcinogenic mechanisms including angiogenesis, cell proliferation, metastasis, and alterations in sex steroid hormone levels. These adipokines are of two

* Corresponding authors. Address: Department of Pathology, CSM Medical University, Lucknow, India. Tel.: +91 961 6021699 (R. Tewari), tel.: +91 522 2613894 (S. Rajender).
E-mail addresses: reshutewarikgmu@gmail.com (R. Tewari), rajender_singh@cdri.res.in (S. Rajender).

1043-4666/$ - see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.cyto.2013.04.008

categories: insulin antagonists (tumor necrosis factor-α, interleukin-6 and resistin) and insulin sensitizers (leptin and adiponectin) [13]. We have recently reviewed the literature regarding the association of diet and obesity with prostate health [14]. It is apparent that certain diet types and excess adipose tissue significantly change the level of circulating bioactive messengers, affecting the risk of prostatic problems. Since adipose tissue is now being regarded as hormonally active tissue; high body fat, obesity, and metabolic syndrome could affect prostate health, by affecting pro-inflammatory and anti-inflammatory cytokines [15,16].

The adipokines, including leptin, adiponectin and interleukin (IL-6), can act both locally through autocrine and paracrine mode and systemically through endocrine pathways [17,18]. Several properties of adipokines could influence prostate carcinogenesis, in particular progression. Insulin sensitizer adipokines (leptin and adiponectin) promote the action of insulin on cellular glucose uptake and decrease the fatty acid metabolism [13]. Leptin is released from adipocytes and its expression is directly related to the lipid content of the cells [19]. Leptin has a role in the regulation of body weight and influences cellular differentiation and CaP progression [19]. It has been observed that leptin is increased in obese subjects and higher leptin levels may increase the risk of advanced CaP [20]. However, it is not clear whether leptin is an independent risk factor or it is a risk factor in association with obesity. Adiponectin is known to have anti-atherogenic, anti-inflammatory and diabetic properties, and its serum level is decreased in abdominal obesity, coronary artery disease and several malignancies related to obesity [21,22]. Circulating adiponectin levels are not only lower in prostate cancer, but also are negatively associated with histologic grade and stage of the disease. Data provide evidence that adiponectin may be related to prostate cancer aggressiveness, although the direction of the association may depend on the extent of adiposity and on cancer grade [23]. Most of the studies indicate that in obese persons leptin may potentiate the growth of cancer cells, and adiponectin may have an opposing effect [12]. It has been speculated that higher leptin levels and low adiponectin levels in sera of obese cancer prostate patients may be the risk factors for aggressiveness and progression of prostate cancer that can have an impact on disease management in these patients.

Insulin antagonist adipokines antagonize the action of insulin. IL-6 and TNF-α both are inflammatory cytokines, released by adipose tissue stimulated by inflammatory stimuli. Studies suggest that serum concentrations of IL-6 and TNF-α are elevated in obesity and weight loss results in decreased levels [24]. These correlate with body mass index (BMI) and predict the development of insulin resistance. Insulin resistance is said to alter the risk of CaP through several biologic pathways including the obesity-sex hormone pathway [8] and non-insulin related pathway [25]. Plasma IL-6 has been demonstrated to have strong relationship with obesity and insulin resistance in comparison to TNF-α. Resistin antagonizes insulin action and its expression is inhibited in obesity and insulin resistance [26]. The physiological role of resistin and the mechanism by which it neutralizes insulin action is not clear. Increased IL-6 levels in obese prostate cancer patients suggest its possible role in cancer progression [1].

Very few studies have examined correlation of adiponectin, leptin and IL-6 in high grade and high stage prostate cancer and BPH [27]. Further, small sample size in the studies has limited the potential to identify risk factors, making it important to conduct further research to confirm the observed association between adiponectin, leptin, IL-6, and the risk of prostate cancer or BPH, and to assess if this association is independent of confounding variables. With this aim, we hypothesized that adipocytokines may affect prostate cancer risk and promotion/progression, and undertook a cross-sectional study to measure BMI, WHR, serum adiponectin, leptin, and IL-6 levels in BPH and prostate cancer.

2. Materials and methods

2.1. Study subjects and design

The investigation was carried out at the Departments of Urology, Surgery, and Pathology of the CSM Medical University, and the Central Drug Research Institute, Lucknow, in a cross-sectional design on histopathologically proven prostate cancer and benign prostatic hyperplasia patients. Patients with urological problems visiting the Department of Urology, King's George's Medical University, Lucknow, were subjected to digital rectal examination (DRE), serum PSA (prostate specific antigen) level measurement, ultrasonography, digital rectal examination (DRE), abdominal/TRUS USG, and urine-flow tests by expert urologists. Patients with serum PSA greater than 4 ng/ml or/and abnormal DRE were asked to undergo ultrasound-guided needle biopsy. The biopsied tissue samples were sent for histological examination and upon histological confirmation of prostate adenocarcinoma or BPH; the subjects were recruited in the study. Only the patients having prostate cancer or BPH were included in the study. Patients having any chronic disease like HIV/AIDS, tuberculosis, or major endocrinopathies were excluded. Five ml of blood sample was collected from each participant, 3 ml of which was used for estimation of glucose, insulin and lipid profile. Two ml plasma/serum was separated and stored at −20 °C for estimation of IL-6, adiponectin, leptin level, and androgens. A total of 95 BPH and 95 prostate cancer patients were selected after screening 270 patients. CaP patients were categorized into high grade ($N = 62$) and low grade ($N = 33$), and high stage ($N = 31$) and low stage ($N = 64$) groups.

2.2. Comparison between BPH and CaP patients

The age of the patients was almost similar in both BPH (65.66 ± 10.66) and CaP (66.54 ± 7.11) groups (Table 1). The level of BMI was significantly ($p < 0.001$) higher in CaP patients (26.58 ± 4.76) in comparison to BPH (22.15 ± 2.90). Similarly, the waist to hip ratio was also significantly ($p < 0.0001$) higher in CaP group (1.08 ± 0.37) in comparison to BPH (0.86 ± 0.15). The levels of leptin (BPH: 25.60, CaP: 56.00) and II-6 (BPH: 9.90, CaP: 32.30) were significantly higher in CaP patients as compared to BPH (Table 2). However, adiponectin level was significantly ($p < 0.0001$) lower in CaP patients (Median = 14.40) in comparison to BPH (Median = 116.08) (Table 2).

Table 1
Comparison of anthropometric parameters between BPH and CaP groups.

Anthropometric measurement	BPH ($n = 95$) Mean ± SD	CaP ($n = 95$) Mean ± SD	P-value*
Age	65.66 ± 10.66	66.54 ± 7.11	0.51
BMI	22.15 ± 2.90	26.58 ± 4.76	<0.001**
WHR	0.86 ± 0.15	1.08 ± 0.37	<0.0001**

* Unpaired t-test.
** Significant.

Table 2
Comparison of adipocytokines levels between BPH and CaP patients.

Adipocytokines	BPH ($n = 95$) Mean ± SD (Median)	CaP ($n = 95$) Mean ± SD (Median)	P-value*
Adiponectin	114.87 ± 13.22 (116.08)	18.64 ± 20.23 (14.40)	<0.0001**
Leptin	37.51 ± 23.13 (25.60)	55.48 ± 40.26 (56.0)	<0.0001**
Il-6	11.52 ± 7.31 (9.90)	34.08 ± 13.41 (32.30)	<0.0001**

* Mann–Whitney U test.
** Significant.