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COMBINATION OF NOVEL DIAGNOSTIC BIOMARKERS FOR PROSTATE CANCER PROGNOSTICATION: IS IT HIGH TIME TO CHANGE?

Biochemistry

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ABSTRACT

Introduction: There is an urgent need of identification of a pool of biomarkers for the early detection of cancer. Correlation between IFN-γ and IL-6 suggests that these cytokines collectively may serve as diagnostic biomarkers for prognostication of PCa. Early detection of prostate cancer by PSA screening remains controversial; yet, changes in PSA threshold, frequency of screening, and addition of other biomarkers have potential to minimise over diagnosis associated with PSA screening. Several new biomarkers appear promising in individuals with elevated PSA levels or those diagnosed with prostate cancer.

Material and Methods: A cross-sectional study was conducted to test the hypothesis of an association of IFN-γ, IL-6 and PSA with obesity parameters for the severity of prostate cancer. Anthropometric examination and hormonal test were also performed simultaneously, of the 100 patients enrolled, 50 were included in BPH and 50 in PCa groups respectively.

Results: Waist hip ratio was significantly ($p<0.0001$) higher in the patients of PCa (1.08±0.37) as compared to BPH (0.86±0.15). Level of IFN-γ was significantly ($p<0.0001$) higher in PCa (142.2±47.6) patients as compared to BPH patients (59.30±9.80). Similarly, the Interleukin-6 level was significantly ($p<0.0001$) higher in PCa patients (34.90±9.30) as compared to BPH patients (11.5±7.40).

Conclusion: Analysis of IFN-γ, IL-6 and PSA levels in our study, suggests a positive correlation of these biomarkers with the severity of PCa. Analysis of this panel of blood-based biomarkers in future studies would be a significant step towards fingerprinting of the biologic behavior of the tumor. This will lead to individualized monitoring and therapeutic approach in future.

KEYWORDS

Prostate cancer, prostate-specific antigen, Interleukin-6, Interferon-gamma

INTRODUCTION:

Prostate cancer (PCa) is the second most common cause of cancer and the sixth leading cause of cancer death among men worldwide. The worldwide PCa burden is expected to grow to 1.7 million new cases and 499 000 new deaths by 2030 simply due to the growth and aging of the global population. [1] Previously it was thought, that prevalence of prostate cancer in India is far lower as compared to the western countries but with the increased migration of rural population to the urban areas, changing life styles, increased awareness, and easy access to medical facility, more cases of prostate cancer are being picked up and it is coming to the knowledge that we are not very far behind the rate from western countries. [2]

Fortunately, the majority of prostate cancers tend to grow slowly and are low-grade with relatively low risk and limited aggressiveness. [3] There are no initial or early symptoms in most cases, but late symptoms may include fatigue due to anemia, bone pain, and paralysis from spinal metastases, and renal failure from bilateral ureteral obstruction. Diagnosis is primarily based on prostate-specific antigen (PSA) testing, and transrectal ultrasound-guided (TRUS) prostate tissue biopsies, although PSA testing for screening remains controversial. Newer diagnostic modalities include free and total PSA levels, PCA3 urine testing, Prostate Health Index scoring (PHI), the"4K" test, genomic analysis, MRI imaging, PIRADS scoring, and MRI-TRUS fusion guided biopsies. [4]

Prostate-specific antigen, or PSA, is a protein produced by normal, as well as malignant, cells of the prostate gland. The PSA test measures the level of PSA in a man's blood. The blood level of PSA is often elevated in men with prostate cancer. In addition to prostate cancer, a number of benign (not cancerous) conditions can cause a man's PSA level to rise. The most frequent benign prostate conditions that cause an elevation in PSA level are prostatitis (inflammation of the prostate) and benign prostatic hyperplasia (BPH) (enlargement of the prostate). There is no evidence that prostatitis or BPH leads to prostate cancer, but it is possible for a man to have one or both of these conditions and to develop prostate cancer as well. [5]

So, there has been a single target approach to discover and validate novel PCa biomarkers. [6]More than thirty types of cytokines have been identified and their biological functions studied by several previous studies. Specific cytokine network formed by each cytokine may coordinate various biological events, including immunity, cell differentiation, proliferation and cancer growth in humans. [7-10] Inflammation is associated with a complex molecular mechanism involving a variety of proinflammatory cytokines. Cumulative evaluation of various cytokines could be a significant step for a better understanding of the pathophysiology and complications of PCa. [10] Various studies show a relation of increase in PSA levels with the aggression of PCa. [11]

Cytokines such as Interleukin-1(IL-1), Interleukin-2 (IL-2), tumor necrosis factor alpha (TNF-α), Interleukin-6 (IL-6) and Interferon-gamma (IFN-γ) are intermediaries of the inflammatory response. [12] IFN-γ is a critical factor in the pathogenesis of prostatic diseases, in the support of the responses of innate and adaptive immunity this cytokine plays a significant physiological part. [13] Controlling the expansion of tumor cells by organized cellular responses against neoplastic cells specifically done by IFN-γ. [14]

Cellular level involvement of IL-6 with the processes of cancer control is reflected by the results of serum studies of cancer patients, where IL-6 may be a sign of diagnosis and tumor load. [15] Increased IL-6 levels have been associated with an advanced stage of cancer and metastasis-related morbidity. [16,17] Most studies published in prostate cancer link IL-6 and tumor aggressiveness. [18,19] Anti-apoptotic effect of IL-6 in prostate cancer is mediated by the Mcl-1 oncogene. [20] The expression of Mcl-1 is also elevated in human prostate cancer tissues.

A biomarker may replicate disruption of a biochemical pathway by a particular mechanism. Given the complexity of the molecular abnormalities associated with PCa, it is questionable that a single marker can accurately segregate tumors of similar clinico-pathologic phenotypes into distinct prognostic categories. Therefore, combinations of independent, yet parallel markers, may provide a more particular prediction of outcome compared to a solitary marker. [21] Thus, studies addressing the role of IFN-γ in prostate cancer are needed to confirm their clinical expediency, especially focus on the innovation of new biomarkers for the detection of this pathology. To observing the high incidence of PCa, the aim of this study is to determine there is a critical need of panel of biomarkers for early detection of cancer. Correlation between IFN-γ, IL-6 and PSA levels,

suggesting the hypothesis that these cytokines collectively may serve as a potential biomarker for the early detection of prostate cancer.

MATERIAL AND METHODS:

A cross-sectional study was conducted to test the association of IFN-γ, IL-6 and PSA with obesity parameters to check the severity of prostate cancer patients. 50 men diagnosed with prostate cancer and 50 men with BPH, were evaluated and the following assessments were done.

Inclusion criteria

All male patients reporting to the Urology outpatient department, during the study period, who were

- 1. Between the ages of 40 and 70 years and
- 2. PCa diagnosed only by histopathology and BPH.

Exclusion Criteria:

Patients suffering from diabetes, chronic liver, kidney, heart disease those taking lipid-lowering drugs or 5-alpha reductase inhibitors were excluded from the study leaving only 50 patients who were included.

Anthropometric examination and blood sampling:

All men underwent a physical examination to measure the height, weight and body mass index (BMI). WHR was calculated from waist circumference at umbilicus divided by hip circumference at greater trochanter and a cut off of 0.9 was taken to categorize central obesity.

Hormonal and biochemical Assessment:

Serum samples of men with suspicion of prostate cancer based on high prostate specific antigen (PSA) and/or abnormal DRE were withdrawn before biopsy between 8 a.m. and 11 a.m. Serum PSA, IFN-gamma and IL-6 levels were estimated using ELISA on the same day. The serum was separated, aliquoted and kept frozen at -80ºC for analysis. The study protocol was approved by the Institutional Review Board for ethical clearance. All participating subjects were informed about the purpose of the study and provided written informed consent.

Staging and grading:

The Gleason grading was done on biopsy tissue and based on score patients were divided into Group 2A: Gleason scores ≥ 6, Group 2B: Gleason score <6.

Statistical Analysis:

Descriptive statistics were used to characterize the study population in terms of frequency and percent, or median and inter-quartile range. The software used was SPSS (version 25), a p value <0.05 was considered as significant.

Results:

A total of 100 patients were included in the study. Out of these, 50 patients were in BPH and 50 in PCa group. The age of the patients was almost similar in both BPH (65.66±10.66) and PCa (66.54±10.11) groups. The level of BMI was significantly (p<0.001) higher in the patients of PCa (25.78±7.76) as compared to BPH (22.15±7.90). Similarly, the waist-hip ratio was also significantly (p<0.0001) higher in the patients of PCa (1.08±0.37) as compared to BPH (0.86±0.15). Similarly, the Interleukin-6 level was significantly (p<0.0001) higher in PCa patients (34.90±9.30) as compared to BPH patients (11.5±7.40). Level of Interferon-gamma was significantly (p<0.0001) higher in PCa (142.2±47.60) patients as compared to BPH patients (59.30±9.80). (In table 1).

Table 1: Comparison of parameters between BPH and PCa patients

Parameters	BPH(n=50) Mean ±SD	PCa(n=50) Mean ± SD	p-value*
Age	65.66±10.66	66.54±10.11	0.51
BMI	22.15±7.90	25.78±7.76	<0.001**
WHR	0.86±0.15	1.08±0.37	<0.0001**
PSA (ng/ml)	27.30±9.5	89.8±11.90	0.001
IL-6 (pg/ml)	6.5±0.74	8.90±0.83	<0.05*
IFN-γ	59.3±9.8	142.2±47.6	<0.0001**

In table 2, the age of the patients was almost similar in both Lower (66.58±10.28) and Higher (66.52±10.08) grades. The level of BMI was significantly (p=0.008) higher in the patients of Higher grade (26.30±5.92) as compared to Lower (24.80±3.83) grade. The higher-grade patients had more risk of being overweight than the lower grade patients (Unadjusted OR=1.14, 95%CI=1.03-1.16). Similarly, the waist-hip ratio was also significantly (p=0.03) higher in the patients of Higher grade (1.27±0.47) as compared to Lower grade (1.07±0.33).

Table 2: Comparison of parameters between Low grade and High-grade patients

Parameters	High grade PCa (n=31) Mean± SD	Low grade PCa (n=19) Mean± SD	p-value*
Age	65.66±10.66	66.54±10.11	0.51
BMI	26.30±5.92	24.80±3.83	<0.04
WHR	1.27±0.47	1.07±0.33	<0.07
PSA	96.50±38.17	78.9±44.05	0.16
IL-6	39.8±16.88	27.2±7.39	<0.001**
IFN-γ	239.80±29.8	219.1±90.20	<0.02

The Higher-grade patients had almost 4 times more risk of having a high WHR level than the lower grade patients (Unadjusted OR=1.14, 95%CI=1.03-1.16). The level of interferon-gamma was significantly (p<0.0001) lower in low-grade patients (Median=4.95) as compared to high-grade patients (Median=10.51). The IL-6 level was significantly lower (p<0.0001) in low-grade PCa patients as compared to high-grade patients (Table-2). The risk of having a higher level of PSA in high grade than Low grade patients. Interferon-gamma levels were significantly Higher (p=0.02) in High grade (Median=8.67) PCa patients as compared to Low-grade patients (Median=6.60).

The age of the patients was almost similar in both Stage-III (66.54±10.11) and Stage-IV (65.66±10.66) patients. The level of BMI was insignificantly (p=0.10) higher in the patients of Stage-III (26.60±5.30) as compared to Stage-IV (25.20±5.22) patients. The Stage-III patients had 8% higher risk of being overweight than the Stage-IV patients (Unadjusted OR=0.92, 95%CI=0.84-1.02). However, the waist-hip ratio was significantly (p<0.0001) higher in the patients of Stage-IV (1.37±0.44) as compared to Stage-III (0.89±0.16) patients. The Stage-IV patients had almost 4 times higher risk of having a high WHR level than the Stage-III patients (Unadjusted OR=3.74, 95%CI=2.68-15.67). Level of PSA in Stage-IV patients is significantly (0.0001) higher as compared to Stage- III patients. Similarly, the level of IL-6 was significantly higher (p=0.003) in the patients of Stage-IV (Median=7.58) as compared to Stage-III (Median=9.05) patients. Level of Interferon-gamma was insignificantly higher in both Stage- IV patients as compared to Stage-III patients (In table 3).

Table 3: Comparison of parameters between Low stage and High stage patients

Parameters	High stage PCa (n=31) Mean± Sd	Low stage PCa (n=19) Mean± SD	p-value*
Age	65.66±10.66	66.54±7.11	0.51
BMI	25.20±5.22	26.60±5.30	0.98
WHR	1.37±0.44	0.89±0.16	0.0001
PSA	113.50±30.10	47.7±16.1	0.012
IL-6	39.8±16.88	28.18±9.4	0.003
IFN-γ	236.40±105.61	210.1±149.32	0.182

DISCUSSION:

The identification of biomarkers, assessable in blood samples, in patients affected by PCa and BPH could be useful in order to differentiate those common prostate diseases as well as to identify specific therapeutic strategies. Patterns of inflammation and endothelial activation seem to offer a biological link between pathogenesis and clinical symptoms of prostatic disease as well as might predict the onset and progression of both PCa and BPH. Several studies support a close relation between BPH and the inflammatory pattern, as suggested by the increased rate (61%) of signs of chronic inflammation in prostates of greater volume (80-89 mL) respect to small ones. [22] As prostate size is a valuable predictor of BPH progression, the relationship between prostate size and chronic inflammation should be indicative of worsening clinical development. Clinical evidence reports that chronic inflammation represents a key condition leading to prostate enlargement and to an increased symptom score as well as a major risk of complications. [23] Furthermore, when inflammation is clinically supposed and then proven histologically, it may be taken into account in the management and treatment of BPH.

Contradictory reports stating either inverse or no correlation between BMI/obesity parameters and BPH. Zucchetto et al observed that

overweight was modestly but inversely related to BPH (Zucchetto et al, 2005) and BMI and waist circumference at evaluation was inversely associated with BPH risk. [24] A potential weakness of the study is the lack of precise clinical definition of BPH. This could result in a bias in the study due to the presence of undetected BPH cases in the control group. Another compounding factor could be that PSA estimation was not a common screening practice in Italy at that time.

In our study, WHR, but not BMI as a measure of obesity, was associated with the elevated prostate volume. This could be explained by the fact that since abdominal obesity is common in India, WHR is a more efficient predictor of obesity than BMI there and more closely correlates with the various hormonal and metabolic sequelae of obesity. In our study, the age of the patients was almost similar in both BPH (65.66±10.66) and PCa (66.54±10.11) groups. The level of BMI was significantly ($p<0.001$) higher in the patients of PCa (25.78±7.76) as compared to BPH (22.15±7.90). Similarly, the waist-hip ratio was more significantly ($p<0.0001$) higher in the patients of PCa (1.08±0.37) as compared to BPH (0.86±0.15). We profiled serum cytokine levels & PSA levels in patients with a high and high stage of PCa. Previous studies have shown that more than thirty types of cytokines have been discovered and their biological functions studied. Each cytokine forms a cytokine set-up, and this set-up may coordinate various biological actions, counting immunity, cell differentiation, proliferation and cancer growth in humans. Thus, the assessment of various cytokines could be significant in gaining a healthier perceptive of the pathophysiology of Pca. [25]

IL-6 is a pleiotropic cytokine and one of the main mediators of the acute phase reaction, produced by fibroblasts, activated macrophages or monocytes, activated T and B cells, endothelial cells, stromal cells. [26] Besides, dysregulation of the immune response in BPH may occur via elevated expression of pro-inflammatory IL-17 which stimulates, in turn, IL-6 and-8 production responsible for stromal growth factor.[27] According to these suggestions, we found IL-6 to be increased systemically in BPH respect to control group. This result confirms the involvement of IL-6 in the onset of BPH and could suggest its possible significance in discriminating prostate inflammatory hypertrophy in comparison normal gland tissue.

Our results confirm the findings of previous studies and add to the literature by documenting the significance of IL-6 and IFN- as predictors of progressive disease. We postulate that serum IL-6 and IFN- levels might be useful prognostic markers about progression to biochemical or symptomatic relapse based on the results of serial measurements. To our knowledge, this is the first time in the reported literature that monitoring of serial serum concentrations of these cytokines has been suggested as possible indicators of disease progression. However, the multivariate regression analysis failed to confirm these cytokines as significant independent prognostic variables for patient survival. IL-6 is known to promote the proliferation and metastatic potential of cancer cells. [28] This cytokine has been characterized as a prostate exocrine gene product that interacts with its receptor in prostate cells, regulating proliferation and differentiation, and in prostate cancer cell lines activates androgen receptor (AR).

Interferon-γ (IFNγ), a potent cytokine known to modulate tumor immunity and tumoricidal effects, is highly elevated in prostate cancer (PCa) patients after radiation. IFNγ is known to modulate cancer immunity and increase cytotoxicity. [29] In addition, IFNγ was able to induce the expression of Slug and ZEB1, both are potent EMT transcription factors, in PCa cell lines C4- 2 and PC3 cells in a dose-dependent manner. Previously identified DAB2IP as an EMT inhibitor in PCa. Thus, we believe that the mechanism of IFNγ-induced EMT is mediated through DAB2IP regulated pathway. Since emerging evidence demonstrates a critical role of miRNA in EMT process, a significant reduction of miR-363 (1176 folds decrease) was detected in DAB2IP-knockdown (KD) cells. The down-regulation of miR-363 in DAB2IP-KD cells was further validated in immortalized normal prostatic epithelial cell (RWPE1 and PNT1A) and PCa lines (LAPC-4 and PC3). Ectopic expression of DAB2IP in C4-2Neo or LAPC4-KD cells was able to induce mature miR-363 levels, indicating that DAB2IP could modulate miR-363 expression. [30]

CONCLUSIONS:

The introduction of total PSA in clinical practice has resulted in early detection and reduced mortality from PCa. However, PCa screening remains controversial, because of the risk of over diagnosis reduced mortality and overtreatment and the inability to detect a significant proportion of dangerous tumors. A large concerted effort has been made to improve and/or monitoring the activity of PCa and to guide molecular targeted therapy and/or assess therapeutic response. An integrated approach with blood-based measurement of different molecular forms of PSA in combination with genetic and urine biomarkers hold the promise of improving screening for and diagnosis of PCa. Analysis of panels of blood-based biomarkers will be a significant step towards fingerprinting of the tumors biologic behavior. This will lead to individualized therapy and monitoring. Further, the emergence of new therapeutic approaches for PCa cannot prosper without a set of markers for prognosticators, predictors, therapeutic targets, and/or surrogate endpoints.

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