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Original Research Article

Interleukin-6 (IL-6) As an Alternative Biomarker of Carcinoma Prostate

Happy Chutia
Senior Resident, Dept of Biochemistry
North East Indira Gandhi Institute of Health and Medical Science (NEIGRIHMS)

Correspondence Email: happy.chutia@gmail.com

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ABSTRACT

Introduction: Interleukin-6 (IL-6) is a multifunctional cytokine that was identified originally as a stimulating factor for B-lymphocytes by virtue of its ability to drive differentiation of B cells into antibody-producing plasma cells. IL-6 stimulates the development of prostate carcinoma as well as production of prostate specific antigen (PSA) and progression of prostate cancer .The purpose of this study was therefore to look if IL-6 as could be used as an alternative biomarker for carcinoma prostrate.
Methods: The study was carried out in diagnosed twenty-five Benign Prostatic Hyperplasia (BPH) and fifteen carcinoma (Ca) Prostate patients. Serum levels of total-prostate specific antigen (total-PSA), free - prostate specific antigen (free-PSA) and IL-6 were assayed by chemiluminiscence method.
Results: In BPH, total PSA, free PSA and IL-6 levels were 6.33±3.47ng/ml, 1.33±.77ng/ml and 3.51±3.03 pg/ml respectively. In Ca Prostrate total PSA, Free PSA and IL-6 were found to be 93.44 ± 22.58 ng/ml, 15.28±3.81 ng/ml and 13.17 ± 4.15 pg/ml respectively.
Conclusion: IL-6 was found to be significantly higher in Ca Prostrate patients as compared to BPH patients. IL-6 can be considered as alternate marker to distinguish between BPH and Ca Prostrate patients and IL-6 receptors may be used as a target in treatment of Ca Prostate patients.
Key words: Benign Prostatic Hyperplasia (BPH), Carcinoma Prostate (CaP), IL-6, total-PSA, free-PSA

INTRODUCTION

Interleukin-6 (IL-6) is a multifunctional pleiotropic cytokine that was identified originally as a stimulating factor for B-lymphocytes by virtue of its ability to drive differentiation of B cells into antibody-producing plasma cells. [(1)] IL-6 is also involved in malignant transformation and tumour progression as shown by several studies. [(2, 3)] The IL-6 receptor is expressed in tissues of epithelial and mesenchymal origin. [(4)] It consists of the two subunits, the ligand-recognizing component (a-subunit) gp 80, and the signal-transducing component (β-subunit) gp 130. [(5)] Binding of IL-6 to the a-subunit leads to dimerization of the gp130 and subsequent activation of Janus kinases. This leads to induction of tyrosine phosphorylation and then nuclear translocation of signal transducers and activators of transcription factors and initiation of gene transcription. [(5)] IL-6 may act both as a positive and as a negative growth factor in target cells.

Prostate specific antigen (PSA) is still the best available tumour marker in

prostate cancer, but presents some limits. PSA is a marker organ-specific, with high sensitivity but low specificity for the detection of cancer prostate. Conditions that can lead to a temporary increase of serum PSA levels not related to tumour processes are manipulations of the prostate gland (per rectal examination or biopsies) and benign diseases (hyperplasia).[6,7] Although prostate cancer is associated with a higher increase in PSA serum levels per gram of tissue than BPH, the overlap in PSA levels between those with BPH and those with prostate cancer remains extensive. [8]

In addition, normal levels have also been observed in patients with tumour pathology. In this way, PSA is not indicative of the evolution grade of disease. [9] In this way, PSA is not indicative of the evolution grade of disease. Therefore, there is a need for novel markers in the detection and management of Ca Prostate. At the present, several researches are going on in search of some new biochemical markers that can detect carcinoma prostate and its prognosis. There are also evidences which show that, IL-6 also stimulates the development of prostate carcinoma. [10] In addition, pro-inflammatory cytokines like IL-6 was related to the production of PSA and progression of prostate cancer. [11, 12]

This study was therefore undertaken to evaluate, if IL-6 could be used as an alternative biomarker for carcinoma prostrate.

MATERIALS AND METHODS

This cross-sectional study was carried out among 25 diagnosed BPH patients and 15 histologically confirmed Ca Prostrate patients attending urology department of North East Indira Gandhi Institute of Health and Medical Science (NEIGRIHMS). Blood samples were collected from the patients and serum total-PSA, free-PSA and IL-6 were estimated. Patients having active infection and prostratitis were excluded. Digital rectal examination was avoided prior to sample collection. None of the patients were receiving any medical or surgical treatment for BPH as well as for Carcinoma prostate. Serum total-PSA, free-PSA and IL-6 were assayed by chemiluminiscence method (Access2, Beckman coulter).

A database was constructed on Microsoft Excel 2007, and statistical analyses were performed using SPSS software version 20. Student's t-test and Pearson Correlation test were performed to analyze the data.

RESULTS

In this study blood samples were collected from 25 BPH patients (aged from 53-84 years) and 15 Ca Prostrate patients (aged from 60-80 years). In BPH patients, total PSA, free PSA and IL-6 levels were 6.33$\pm$3.47ng/ml, 1.33$\pm$.77ng/ml and 3.51$\pm$3.03 pg/ml respectively. In Ca Prostrate total PSA, Free PSA and IL-6 were found to be 93.44 $\pm$ 22.58 ng/ml, 15.28$\pm$3.81 ng /ml and 13.17 $\pm$ 4.15 pg/ml respectively.

A highly significant increase in serum total PSA and free PSA levels were found in Ca prostrate patients as compared to BPH patients ($p < 0.001$). A highly significant increase in serum IL-6 level was also found in Ca prostrate patients as compared to BPH which means that IL-6 is also capable of differentiating between BPH and Ca prostrate patients.

No statistically significant correlation was found between serum total PSA and IL-6 and between serum free PSA and IL-6.

Table1: Biochemical parameters of the study group.

	Reference range	BPH	Ca Prostrate	p value
Number of subjects		25	15	
Serum Total PSA	0-4 ng/ml	6.33±3.47	93.44 ± 22.58	<0.001
Serum free PSA	.2- 4 ng/ml	1.33±.77	15.28±3.81	<0.001
Serum IL-6	5.3-7.5pg/ml	3.51±3.03	13.17 ± 4.15	<0.001

DISCUSSION

In this study serum total PSA and free PSA in BPH patients was significantly lower than that in Ca prostrate patients. Though in BPH patients, average serum level of both total and free PSA levels were below 10ng/ml, which is considered as the cut off level to differentiate between benign enlargement and carcinoma prostrate, [10,13] 3 patients out of 25 had higher serum total PSA level (>10ng/ml). In Ca prostrate patients, average serum level of both total and free PSA level was above 10ng/ml. All the 15 Ca prostrate patients had serum total PSA levels >10ng/ml.

Serum IL-6 levels were within normal range in all the BPH patients. While in Ca prostrate patients except 3 patients out of 15, serum IL-6 levels were above the normal range.

Moreover, highly significant increase in serum IL-6 levels in Ca prostrate patients was found as compared to BPH patients. This finding correlated with the studies done by Jose Ramon Cansino Alcaide *et al* [10] and Jun Nakashima *et al.* [14] However, there was no significant correlation between serum free and total PSA and serum IL-6 levels.

IL-6 acts as a paracrine growth factor and as an autocrine growth factor for prostate cancer cells. [15] There are studies which showed that serum IL-6 level is a significant prognostic factor for prostate cancer. [10, 14]

IL-6 can be considered as alternate marker to distinguish between BPH and Ca Prostrate patients and in follow up of Ca Prostrate patients as well. Moreover, as IL-6 receptors are expressed in prostate cancer cells and IL-6 was related to the production of PSA and progression of prostate cancer, these receptors can be taken as a target for the treatment of Carcinoma Prostrate.

Limitation of this study includes small study group, lack of long term follow up, no intervention with IL-6 receptor targeting and study to see its outcome. Therefore a larger study group with active intervention with long term follow up is necessary to corroborate the findings of this study.

CONCLUSION

Some elaborate studies are required for a better understanding of the mechanism and role played by the elevation of circulating PSA related to the serum level of cytokine IL-6. This may also improve clinical management and provide new targets for therapy in these patients.

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