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ROLE OF C-REACTIVE PROTEIN IN PATIENTS WITH BENIGN PROSTATIC HYPERTROPHY AND PROSTATE CANCER

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ABSTRACT

C-Reactive protein (CRP) is a general marker of inflammation correlated with cancer risks and is also reported as a useful biomarker in urologic cancer. Prostate-specific antigen (PSA) is produced exclusively by epithelial cells of the prostate gland and increased serum PSA levels are an important indicator for prostate cancer. In this study we aimed to examine serum CRP levels in men with prostate cancer and benign prostatic hypertrophy (BPH) and finds its association with serum Prostate specific antigen (PSA) level. This case control study was conducted in Department of Biochemistry in association with Department of Urology, VMMC and SJH, New Delhi. Thirty cases of newly diagnosed prostate cancer, thirty cases of BPH confirmed by trans rectal needle biopsy and thirty age and sex matched healthy controls were included in the study. Patients with acute infections, rheumatoid arthritis, gout, asthma, chronic pulmonary disease, myocardial infarction and those who had history of taking nonsteroidal anti-inflammatory drugs were exempted from the research. Serum CRP and PSA level was measured by ELISA. The serum PSA and CRP level of the prostate cancer and BPH patients was significantly higher than controls. But we couldn't find a significant association between CRP level and prostate specific antigen (PSA) level. CRP levels as well as the underlying inflammation, are potentially modifiable so a better understanding of its level and its association with PSA may prove to be a potential target for disease prognosis and therapeutics. Future prospective study should include a larger population of patients for more accurate results.

Key words: Prostate specific antigen (PSA), Highly sensitive C-Reactive protein (hsCRP), Benign prostatic hypertrophy (BPH), Prostate cancer.

INTRODUCTION

Chronic inflammation has long been associated with infection based cancers. C-reactive protein, an acute-phase reactant is a sensitive marker of inflammation [1]. This improved sensitivity of highly sensitive CRP allows hs-CRP to be used to detect low levels of chronic inflammation. A growing body of literature has described a relation between circulating C-reactive protein serum levels and prognosis in tumors like esophageal cancer, cervical cancer, endometrial cancer, ovarian cancer and renal cell carcinoma [2-7].

Several hypothesis has been proposed to define the role of CRP in cancer. First, it has been suggested that elevated hsCRP levels are a result of an underlying cancer. Alternatively, chronic inflammation and elevated hs-CRP might have a causal role in carcinogenesis through oxidative damage by causing irreversible cellular and DNA damage through the generation of free radicals, and the promotion of rapid cellular growth through DNA and cellular replication [8]. Moreover, activation of inflammatory pathways might facilitate tumor progression by promoting cell motility, vascular permeability, and angiogenesis [9-10]. To date, epidemiologic evidence of a diagnostic or etiological role of hs-CRP in cancer has been inconsistent [11].

Prostate cancer (PCa) is the second most common cause of cancer in men worldwide and eight most common

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in india and the fifth leading cause of cancer death among men worldwide (globocan.iarc.fr/). Inflammation plays a crucial role in etiology of prostate cancer as evident from epidemiological, histopathological and molecular pathological studies. But mostly, the cause of prostatic inflammation is unclear. The initial inciting event may include chemical and physical trauma, dietary factors, oestrogens, or a combination of two or more of these factors or a break in immune tolerance, presence of proliferative inflammatory atrophy (PIA), and the development of an autoimmune reaction to the prostate [12]. The presence of inflammatory process seen in radical prostatectomy specimens, prostatic tissues resected during the treatment of benign prostate hyperplasia and tissue samples obtained from prostate needle biopsy, suggests that inflammation and hence CRP may play a role in prostate carcinogenesis [13-14]. Several epidemiologic studies have attempted to find relationship between baseline hs-CRP and the incidence of human carcinomas, and have shown inconsistent associations [15-18]. While some studies reported that in Prostate cancer patients with a higher CRP level was significantly associated with poor prognosis in Prostate cancer [19]. But other studies could not conclusively find any association between CRP and survival in Prostate cancer patients [20].

Prostate-specific antigen (PSA) is produced exclusively by epithelial cells of the prostate gland. Disruption of the cell-to-cell architecture of prostate epithelium leads to increased serum PSA levels [21]. Apart from prostate cancer, nonmalignant conditions and prostate manipulation can also increase its level. Hence CRP along with PSA might prove to be useful in these patients. The aim of the study was to find levels of CRP in BPH and prostate cancer patients and find correlation between PSA and CRP in north Indian population visiting Safdarjung Hospital.

MATERIAL AND METHODS

The study was conducted in Department of biochemistry in association with Department of urology, VMMC and SJH, New Delhi. The present case control study included thirty newly diagnosed cases of prostate cancer histologically confirmed by trans rectal needle biopsy, thirty newly diagnosed BPH patients with elevated PSA level>4ng/ml (histologically negative for cancers) and thirty age and sex matched healthy control. Patients who had acute infections, rheumatoid arthritis, gout, asthma, chronic lung disease, myocardial infarction, or who had taken nonsteroidal anti-inflammatory drugs were excluded from the study because these variables can impact CRP. The healthy controls were randomly selected with respect to age and sex with normal PSA level, with no history of voiding symptoms, prostate surgery, family history of cancer, chronic illness. The study was conducted after ethical clearance from the institute and written informed consent was taken from both cases and control. The case and control group were subjected to structured questionnaire (regarding demographic, medical and lifestyle information). 5ml of venous blood was collected in a plain vial and serum separated within 1hr of collection and stored at -80◦C till further analysis. Serum hs-CRP and alkaline phosphatase (ALP) and Prostate specific antigen (PSA) levels were quantitatively determined by enzyme linked immunoassay using kits. (Calbiotech Pvt Ltd, USA; Beacon diagnostics, India; DRG international Inc., USA)

STATISTICAL ANALYSIS

Selected characteristics were compared between cases and control using the Graphpad prism software. The nonparametric Kruskal Wallis test was used to evaluate differences in CRP level in BPH cases, Prostate cancer cases and healthy controls. Spearman's correlation coefficient was used to see the association between variables.

RESULTS

Thirty diagnosed cases of prostate cancer, 30 cases of BPH and 30 healthy controls were included in the study. The average age was 65.8± 4.5 years (range 50 to 80 years) for healthy volunteers whereas it was 65.7±9.04 years (range, 51 to 80 years) for BPH cases, 68.3±9.28 years (range, 56 to 83 years) for prostate cancer cases. The baseline characteristics are shown in table 1. The median PSA level was5.2 ng/ml(range 4 – 10.8ng/ml) in BPH and 6.9 ng/ml(range 5 –24ng/ml) in prostate cancer cases which was significantly higher compared to control (2ng/ml, range 0.5 - 4 ng/ml). (Table 2) Similarly, the medianhs CRP level of the BPH group 4mg/l (range1-9mg/l) and prostate cancer group 6.5 (range 1.2 -25.4mg/l) was significantly high as compared to controls (1.2mg/l, range 0.9-5mg/l). (Table 3) Moreover, a significant difference was found between CRP levels in BPH and cancer patients. The serum level of ALP was also found to be higher in cases [BPH, 149.5U/l (range135-185U/l); prostate cancer, 167.5 (range116-220U/l)] vs control, 115.5U/l(range 54-147U/l). However, we found no significant correlation between CRP and PSA in cancer and BPH patients (Table 4).

Table 1. Baseline Characteristics of control and patients of BPH and Prostate cancer

	PSA (ng/ml) Control	PSA(ng/ml) BPH	PSA (ng/ml) Cancer	ALP (U/L) Control	ALP (U/L) BPH	ALP (U/L) Cancer	hsCRP (mg/l) Control	hsCRP (mg/l) BPH	hsCRP (mg/l) Cancer
Number of values	30	30	30	30	30	30	30	30	30
Minimum	0.5000	4.0	5.0	54	135	116.0	0.9	1	1.2

25% Percentile	1.000	4.28	6.0	101.5	143.8	152.3	1.75	3.0	5.0
Median	2.000	5.2	6.9	115.5	149.5	167.5	1.8	4.0	6.5
75% Percentile	3.000	6.63	8.0	127.8	162	189.8	3.0	7.25	10.5
Maximum	4.000	10.8	24.0	147	185	220.0	8.0	9.0	25.4
Mean	2.083	5.48	7.56	107.9	153.3	169.6	2.56	5.03	9.08
Std. Deviation	1.094	1.26	3.403	9.3	8.49	7.9	1.59	2.53	5.75

Table 2. Table showing comparison of PSA values between control, BPH and Prostate Cancer patients.

Kruskal wallis test followed by post hoc test	Significant? P < 0.05?	Summary
PSA BPH vs PSA Control	Yes	***
PSA Cancer vs PSA Control	Yes	***
PSA BPH vs PSA Cancer	No	P>0.05

* p<0.05, ** p<0.01, *** p<0.001

Table 3. Table showing comparison of CRP values between control, BPH and Prostate Cancer patients.

Kruskal wallis test followed by post hoc test	Significant? P < 0.05?	Summary
CRP BPH vs CRP Control	Yes	***
CRP Cancer vs CRP Control	Yes	***
CRP BPH vs CRP Cancer	Yes	*

* p<0.05,** p<0.01, .*** p<0.001

Table 4. Table showing correlation between PSAand CRP values between control, BPH and Prostate Cancer patients.

	Spearman correlation	P value
PSA BPH vs CRPBPH	0.049	0.795
Cancer PSAvs CRP Cancer	0.3364	0.069
PSA Control vs CRP Control	-0.024	0.889

* p<0.05, ** p<0.01, *** p<0.001

DISCUSSION

The worldwide Prostate Cancer burden is expected to upsurge due to the growth and aging of the population. The incidence rates of this cancer are constantly and swiftly increasing and the cancer projection data shows that the number of cases will become doubled by 2020 [22].

Correct and complete knowledge of epidemiology and pathogenesis is imperative to plan and formulate sound cancer control strategies before it becomes a far greater public health problem in the future based on scientific and empirical bases. Since inflammation plays a major role in carcinogenesis we tried to investigate the usefulness of CRP and prostate specific antigen (PSA) in BPH and cancer patients and compared to controls.

In the present study PSA level was significantly higher in cases (both BPH and cancer) compared to control but PSA level was comparable between BPH and newly diagnosed cancer patients. Prostate-specific antigen screening has remained controversial because of its risk benefits ambiguity and the, optimal screening strategy. However, PSA levels are prostate-specific but not cancer-specific [23-24]. A common PSA threshold for biopsy has been greater than 4.0 ng/mL [25], a cut point associated with a positive predictive value of about 30% in men aged 50 years or more and a negative predictive value of about 85% in men of median age 69 years [26]. Further, most prostate cancer are relatively harmless, hence PSA screening considerably increases the risk of receiving a diagnosis of prostate cancer, leading to treatment morbidity among men, with meagre of benefit [27]. PSA levels alone are not a reliable discriminator between prostate cancer and benign conditions of the prostate. Nevertheless disadvantage of prostate-specific antigen (PSA) for the early detection of prostate cancer is that many men must be screened, biopsied and diagnosed to prevent one death hence there is an eminent need to increase the specificity of screening for lethal Prostate cancer at an early stage [28]. Moreover, acute inflammation is thought to be the more important contributor to PSA elevation according to previous reports [29-32]. Therefore, we sought to find the hsCRP levels in these subjects to elucidate the causal role of inflammation in prostate cancer. hsCRP level was significantly higher in cases compared to control moreover there was also a statistically significant difference between cancer and BPH groups with respect to their hsCRP levels [33,34,13,21]. Further we tried to find correlation between hsCRP and PSA levels in these patients.

But, we failed to observe a significant correlation between hsCRP and PSA levels in the benign or malignant group as also found by Kim et al. Although some studies [34] found a positive correlation between CRP and PSA. A limitation of this study is the small study population of only 30 BPH and 30 cancer patients. Future prospective

study should include a larger population of patients for more accurate results. Further we need to study correlation between CRP and prostate biopsy specimens to classify pathological inflammation levels. This readily measurable biomarker should be examined in larger studies along with other potential prognostic factors. Recent evidence has suggested that elevated CRP is not only a marker of inflammation and cancer, but also plays a functional role in the proliferation of tumor cells [35]. Nevertheless, CRP levels, as well as the underlying inflammation, are potentially modifiable so a better understanding of how inflammation, and potentially CRP [7] itself, affects cancer pathogenesis, progression and treatment may be helpful in cancer prognosis and therapeutics.

CONFLICT OF INTEREST STATEMENT

The authors declare that there are no conflicts of interest.

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