International Journal of Research and Review
www.ijrrjournal.com E-ISSN: 2349-9788; P-ISSN: 2454-2237

Original Research Article

To Study the Association of Vitamin D and Inflammation in Prostate Cancer Patients of Northern India

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ABSTRACT

Introduction: Prostate cancer is one of the important causes of morbidity and mortality in men worldwide. Inflammation plays an eminent role in cancer CRP is a well-known inflammatory marker and anti-inflammatory and anticancer effect of vitamin D has long been known. Hence, we sought to study the levels of vitamin D levels along with CRP levels in prostate cancer patients.
Materials and Methods: The study was conducted in Department of biochemistry in association with Department of urology, VMMC and SJH, New Delhi. The case control study included forty newly diagnosed cases of prostate cancer patients histologically confirmed by transrectal needle biopsy with elevated PSA level>4ng/ml and forty age matched healthy control. Vitamin D, CRP and PSA levels were estimated and its association seen.
Results: Vitamin D was significantly low and CRP significantly high in prostate cancer patients compared to control. Further the study also found a significant negative association between vitamin D and CRP.
Conclusion: A marked decrease in vitamin D associated with increase in CRP supports the inflammatory etiology of Prostate cancer. It has been known that vitamin D receptors and enzymes are also expressed in human prostate epithelial cells and vitamin D has potential immunomodulatory role. Vitamin D supplementation may prove to be beneficial in prostate cancer patients against the high economic costs of chemotherapy and morbidity of the patients.
Keywords: Prostate cancer, CRP, Vitamin D, PSA, Inflammation

INTRODUCTION

Prostate cancer is the second most common cause of cancer in men worldwide and seventh most common in India and the sixth leading cause of cancer death among men worldwide (globocan.iarc.fr/). [1] There is also emerging evidence that inflammation is crucial for the aetiology of prostate cancer.

Since long time it is suggested that vitamin D as a surrogate for sunlight exposure may protect against colon and prostate cancer risk. [2] Vitamin D, popularly known as the sunshine vitamin plays a key role in the prevention and treatment of cancer besides its classical role in bone metabolism. Several epidemiological, preclinical, and cellular research during the

last decades have proposed diverse mechanism of its anticancer effect. [3,4] Studies suggest that vitamin D can regulate the entire process of tumorigenesis, from initiation to metastasis and cell-microenvironment interactions. [4,5]

Moreover, it has been accepted that chronic inflammation has 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. [6] Moreover, it facilitates tumor progression by promoting cell motility, vascular permeability, and angiogenesis. [5,7,8]

Accumulating data suggest that vitamin D exerts anti-inflammatory effects via at least four mechanisms by inhibiting prostaglandin (PG) pathway, suppressing the p38 MAPK, nuclear factor kappa B (NFκB) mediated pro-inflammatory signaling pathway and by the interaction between immune and cancer cells to suppress the production of pro-inflammatory cytokines (changes from TH1/Th17 to Th2/Treg cell). [5,6,10]

C-reactive protein (CRP) is a non-specific but sensitive marker of acute-phase inflammation. [11] CRP is a surrogate for interleukin 6 (IL-6) action which plays an important role in acute phase of inflammatory responses by inducing hepatocytes to increase the synthesis of CRP and other acute phase proteins.

A growing body of literature has described a relation between circulating C-reactive protein serum levels and prognosis in different tumors. CRP may play a role in prostate carcinogenesis. [12-13] Several epidemiologic studies have attempted to identify associations between baseline hs-CRP and the incidence of human carcinomas, and have shown inconsistent associations. [14]

Prostate-specific antigen (PSA) is produced exclusively by epithelial cells of the prostate gland. Disruption of the cell-to-cell architecture of prostate epithelium results in increased serum PSA levels. [15] Apart from prostate cancer, nonmalignant conditions and prostate manipulation can also increase its level.

Subclinical prostate inflammation is one of the most important factors contributing to elevation of serum PSA levels. Besides, prostate biopsy, there is no other reliable method to detect prostate inflammation. Therefore, we hypothesized that serum C-reactive protein (CRP) a commonly used inflammatory marker might serve as an indicator of intraprostatic inflammation and its implication in cancer.

Therefore the present study aimed to find the association of vitamin D levels with CRP levels in prostate cancer patients to reveal the inflammatory nature of the cancer and to ascertain the role of vitamin d in causation of prostate cancer through its immunomodulatory role in various anti-inflammatory cascades/pathways which further might be useful in monitoring and treatment of these patients.

MATERIALS 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 forty newly diagnosed cases of prostate cancer histologically confirmed by trans rectal needle biopsy with elevated PSA level>4ng/ml (histologically negative for cancers) and forty age and sex matched healthy control. Patients who had acute infections, rheumatoid arthritis, gout, asthma, chronic lung disease, myocardial infarction, or apoplexy 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 CRP, vitamin D level 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

The parameters were not normally distributed; therefore, median and ranges were used to describe distributions between cases and controls. Nonparametric statistics (Mann–Whitney *U* test) were used to compare serum vit D, CRP and PSA levels between patients and controls. Linear regression was used to study association of PSA with CRP and vitamin D in cases and controls. Vitamin p values of <0.05 were considered statistically significant. Statistical analyses were performed using SPSS 22.0 software.

RESULTS

Sixty diagnosed cases of prostate cancer and 60 healthy controls were included in the study. The average age was 65.8± 4.5 years (range 50 to 80 years) for healthy volunteers, 68.3±9.28 years (range, 56 to 83 years) for prostate cancer cases. The baseline characteristics are shown in Table 1.

Table 1: The baseline characteristics of study (40) and control (40) population

Parameters	Cases (Prostate Cancer)	Controls	P value
Age (Years) Median(Q1-Q3)	65.8 (50-80)	68.3 (56-75)	0.65
PSA (ng/ml) Median(Q1-Q3)	8.150 (6.47-12.4)	1.700 (0.8-2.75)	<0.001
Vitamin D (ng/ml) Median(Q1-Q3)	10.35 6.8-16.65)	17.5 (12.8-25.83)	<0.05
CRP (mg/L) Median(Q1-Q3)	2.95 (1.4-5.3)	1.05 (0.6-1.4)	<0.001

P<0.05 Significant

The median and interquartile range for PSA level was 8.150(6.47-12.4) ng/ml in cancer patients compared to 1.700(0.8-2.75) ng/ml in healthy cases. Similarly, the median CRP level was 2.95(1.4-5.3) mg/Lin cases and 1.05(0.6-1.4) mg/L in controls. Whereas median and interquartile range of vitamin D level was estimated to be 10.35 (6.8-16.65) ng/ml and 17.5(12.8-25.83) ng/ml in cancer and control respectively.

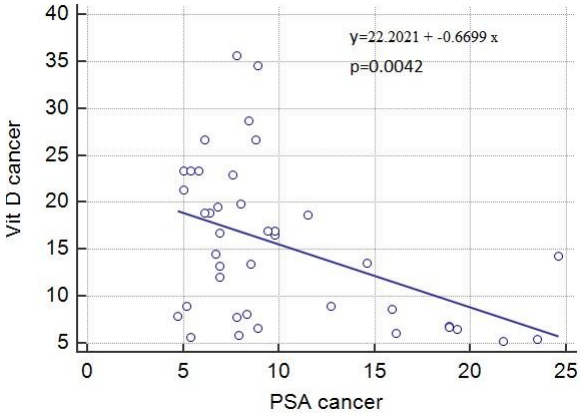

Figure 1: Linear regression analysis showing negative association of Vit D with PSA in 40 Prostate cancer patients. P<0.05 Significant
C reactive Protein (CRP) mg/L, Vitamin D(Vit D) ng/ml, Prostate specific antigen(PSA) ng/ml

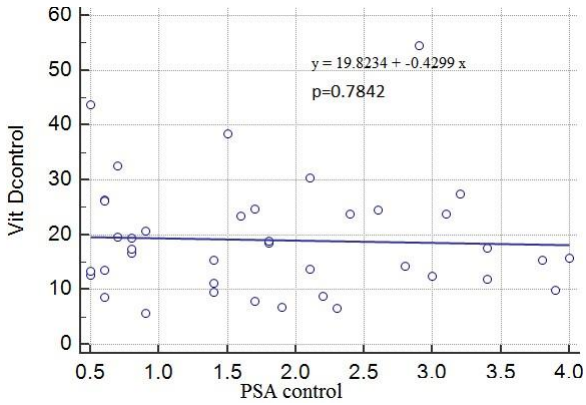

Figure 2: Linear regression analysis showing no significant association of Vit D with PSA in 40 healthy controls.
vitamin D (vit D) ng/ml, Prostate specific antigen (PSA) ng/ml

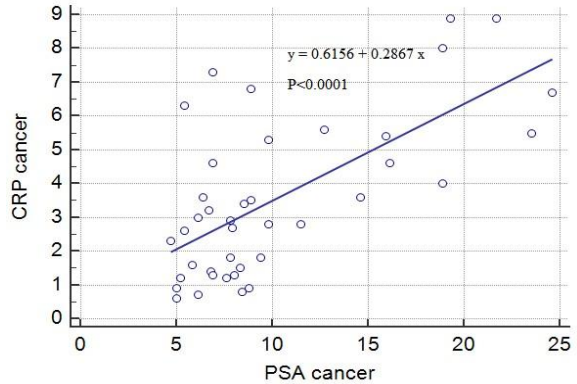

Figure 3: Linear regression analysis showing positive association with PSA in 40 Prostate cancer patients. P<0.05 Significant
C reactive Protein (CRP) mg/L, Prostate specific antigen (PSA) ng/ml

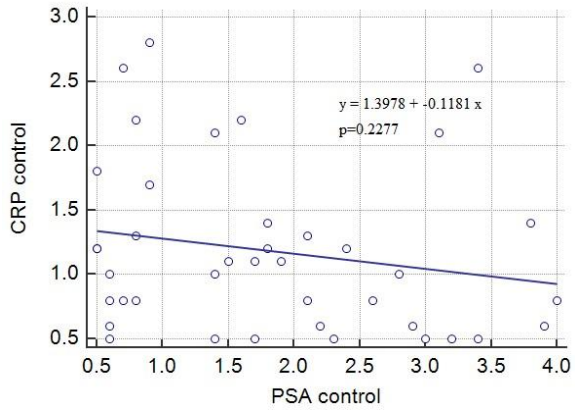

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Figure 4: Linear regression analysis showing no significant association of CRP with PSA in 40 healthy controls.
C reactive Protein (CRP) mg/L, Prostate specific antigen (PSA) ng/ml

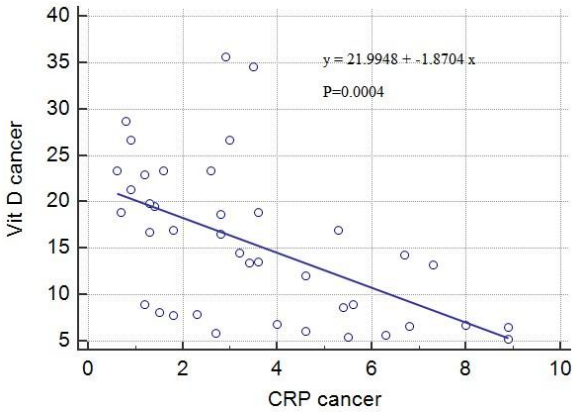

Figure 5: Linear regression showing inverse association between vit D and CRP in 40 Prostate cancer patients. P<0.05 Significant
C reactive Protein (CRP) mg/L, vitamin D(vit D) ng/ml

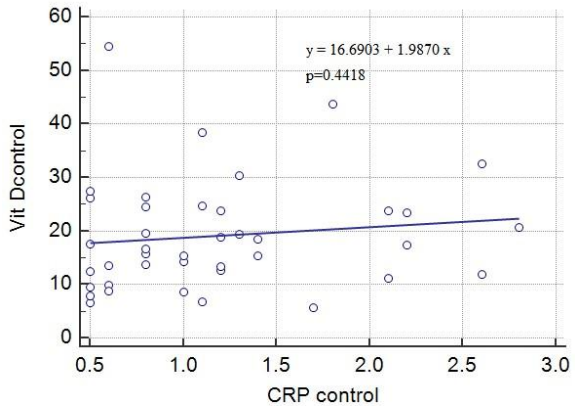

Figure 6: Linear regression showing no significant association between vit D and CRP in 40 healthy controls.
C reactive Protein (CRP) mg/L, vitamin D (vit D) ng/ml

Serum vitamin D level was significantly low and hsCRP significantly high in patients with cancer compared to controls (Table 1). Further, significant negative association between vit D and PSA level was observed in cancer patients (Figure 1) compared to controls (Figure 2). A significant positive association between CRP and PSA levels in cancer was found in linear regression model in cancer patients (Figure 3). But no such significant association was seen in controls. (Figure 4).

We also found significant inverse association between vitamin D and CRP patients in cancer (Figure 5) in contrast to controls (Figure 6).

DISCUSSION

Prostate cancer is the most common cancer among men in developed countries and a leading cause of mortality and morbidity globally. [1] Inflammation plays a crucial role in the aetiology of prostate cancer however in most cases; the cause of prostatic inflammation is unclear. One of the inciting factors in pathogenesis is a break in immune tolerance, presence of proliferative inflammatory atrophy (PIA), and the development of an autoimmune reaction to the prostate. [15]

PIA in the anatomic peripheral zone of the prostate where cancer develop, biopsy results and prostatectomy specimens often indicate the presence of inflammatory tissue. [16] Studies have revealed that regular use of non-steroidal anti-inflammatory drugs may reduce the risk of prostate cancer advocating its inflammatory etiology. Considerable, evidence supports anti-inflammatory role of vitamin D. Immune dysregulation and inflammation are increasingly recognized as viable targets in cancer therapy and prevention.

Hence in this study we measured the serum vitamin D levels. Vitamin D level was significantly lower in patients with prostate cancer compared to control.

The protective effect vitamin D against developing prostate cancer was proposed by Schwartz and Hulka for the first time when they found that the risk of prostate cancer was elevated in the elderly with lower serum vitamin D levels. [17]
Several studies of prostate cancer found a decreased level of vitamin D and statistically significant association, [17-18]

whereas some reported no statistically significant association with prostate cancer. [19-20] A meta-analysis of 21 observational studies found an elevated risk of prostate cancer in subjects with increased 25-hydroxyvitamin D levels. [21]

However, this inconsistency can be accounted by seasonal variation, nature of study, confounding factors, vitamin D receptors (VDR) polymorphisms might be related to the variant risk of prostate cancer. [22]

The low vitamin D status can be due to inflammation mediated oxidative stress in cancer which reduces 25(OH)D concentration, by interfering with key vitamin D metabolizing enzymes, disturbing the liver's biosynthesis of 25(OH)D, increasing oxidative catabolism thus lowering 25(OH)D concentration. [10]

Besides in contrast it has been hypothesized that, that vitamin D decreases inflammation.1,25(OH)2D3 affects both the innate and adaptive immune systems switching from an inflammatory T-helper 1 (Th1)/Th17 response to the less inflammatory Th2/Treg profile. [16,17] In vitro, these effects result in decreased production of pro-inflammatory markers such as: tumor necrosis factor a (TNF-a), interferon gamma (IFN-g), interleukin (IL)-2but with increased production of anti-inflammatory cytokines such as IL-10. [23]

Low vitamin D also favor's cancer by other mechanisms by regulating cell cycle, induction of apoptosis, suppression of the "pro‑proliferative" signaling molecules, Inhibition of angiogenesis, motility and invasion, Induction of differentiation, modulation of the expression of tumor associated growth factors which has been seen in vitro and in vivo in prostate cancer cells. [10,24,25] Besides, older people are comparatively vitamin D insufficient since they are very little exposed to UV light and ability to synthesize vit D decreases with age. [26] Hence low vitamin D is detrimental in cancer and in older age.

Next, we sought to see association between vitamin D and PSA to delineate its role in cancer. Increased serum PSA levels are an important indicator for prostate cancer but PSA levels are prostate-specific but not cancer-specific. We found positive significant association between serum vitamin D levels and PSA levels in cancer patients.

Several studies have seen effect of vit D supplementation on PSA effects which are slow the increase of PSA levels [27-28] or no effect on PSA. [29-30] To summarize, findings regarding the effects of vitamin D on PSA are mixed. [31,32]

The in discrepancy might be a result of small, non-minority patient populations, varied doses and duration, seasonal and genetic makeup and supplementation has been studied. [33]

Further to elaborate the inflammatory pathogenesis of prostate cancer we decided to measure levels of an inflammatory marker CRP and see its association with PSA and vitamin D levels.

CRP levels were significantly higher in patients compared to control. A significant positive correlation between CRP and PSA levels was found in the malignant group, further suggesting a correlation between prostatic inflammation and prostate cancer.

In congruence with our findings, several studies also found a positive correlation between CRP and PSA levels in their prostate cancer patients. [34-36] Besides increased production of CRP by hepatocytes in response to inflammation, local malignant cells also produce increased IL-6 leading to elevated levels of CRP. [36]

However, epidemiological evidence for a diagnostic or an etiological role of circulating CRP in cancer may be inconsistent owing to the pathogenetic heterogeneity of tumor microenvironment, and multiple factors affecting risk between CRP levels and cancer.

The natural course of prostate cancer is difficult to clearly define. There have been studies suggesting a relationship between prostate cancer and inflammation, as prostate biopsy results and prostatectomy

specimens often indicate the presence of inflammatory tissue. [16]

A causal role for chronic or recurrent inflammation or infection in the development of prostate cancer has yet to be confirmed, but inflammation might contribute to carcinogenesis by several interrelated mechanisms. Elaboration of tumorigenic cytokines and growth factors, the induction of cyclooxygenase-2 in macrophages and epithelial cells and generation of mutagenic reactive oxygen and nitrogen species favors inflammation in the form of stromal and epithelial infiltrates of lymphocytes and histiocytes commonly found in the peripheral zone of the prostate, where cancer is mostly seen. [37]

The present study analyzed the association among prostate cancer, vitamin D status and inflammation. Our results showed that serum 25-(OH)D was reduced in patients with prostate cancer. By contrast, serum CRP, a marker of systemic inflammation, was elevated in patients with prostate cancer. Vitamin D was associated with negative and CRP positive association with PSA levels in cancer.

Vitamin D deficiency is widely prevalent and has potential of modulating inflammatory response. Finally, we sought to study whether vitamin D has an inhibitory effect on inflammatory pathogenesis of prostate cancer by assessing the association between serum levels of vitamin D and C-reactive protein**.**

A significant inverse association between vitamin D (anti-inflammatory) and CRP (proinflammatory) levels was seen in prostate cancer patients compared to control. In conclusion, lower levels of Vitamin D are associated with higher levels of C-reactive protein. The result supports low vitamin D levels promote inflammatory role in prostate carcinogenesis.

Similar findings have been reported by Xie et al. [38] Low vitamin D status is reported to simulate mild acute phase response in which cause elevated concentrations of C-reactive protein (CRP), several hemostatic factors and different pro-inflammatory cytokines. These results suggest that low vitamin D status is associated with inflammation in pathogenesis of prostate cancer.

Not many studies have seen association of vitamin D with CRP in prostate cancer. Studies in other diseases and cancer have suggested vitamin D supplementation may reduce circulating CRP levels but reports were inconsistent. [39-41]

It may be stated that heterogeneity across the findings of the studies may be due to supplemental dose of vitamin D, length of the study, seasonal change or geographical location inflammatory factors and never the less heterogeneity of the tumor microenvironment.

Vitamin D is able to affect the immune system that could explain the observed association with CRP. Vitamin D receptors are present in immune cells and inhibits proinflammatory TH1/Th17 profile and promotes Th2/Treg profile(anti-inflammatory) so low Vitamin D leads to inflammation and increase CRP. Vitamin D also inhibits synthesis of IL-6 by monocytes, which is the primary stimulant of CRP production in the liver thereby low vitamin D can also lead to increase CRP production. [42]

The strong association of anti-inflammatory vitamin D and pro-inflammatory CRP with PSA suggests that inflammation might be fundamental in prostate cancer, and prove to be a genuine target for prostate cancer treatment and prognosis.

A detailed understanding of intricate networks involving the oncogenic and vitamin D metabolism pathways, vitamin D receptor polymorphisms, nuclear signaling pathway will contribute to the understanding of dysregulated vitamin D metabolism and function in cancer. Hence, study of vit D and CRP would provide a promising platform for potential personalized therapeutics to study the interplay of signaling network in prostate tumor microenvironment and biochemical

events linking inflammation to prostate cancer.

CONCLUSION

Indeed, supplementation of vitamin D which is a modifiable factor may prove to be beneficial in prostate cancer patients against the high economic costs of chemotherapy and morbidity of the patients.

ACKNOWLEDGEMENT

We acknowledge all the participants in the study, the lab technicians, and staffs in Department of Biochemistry without whose support it would not be possible.

Conflict of Interest: The authors declare that there are no conflicts of interest

Authors' Contributions: All the authors have accepted responsibility for the entire content of this submitted manuscript and approved submission.

Research Funding: The author(s) received no financial support for the research, authorship, and/or publication of this article.

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How to cite this article: Taneja K, Patel S, Sharma A et.al. To study the association of vitamin D and inflammation in prostate cancer patients of northern India. International Journal of Research and Review. 2019; 6(8):1-9.

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