Association of metabolic parameters, lipid and cytokine profiling, androgens and insulin levels in Precancer and Prostate cancer: A cross-sectional study in north Indian set up

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Abstract

Introduction: *Prostatic diseases are highly prevalent in men worldwide among which Prostate cancer (PCa) is a significant cause of morbidity and mortality especially in many western countries and second leading cause of death in India. Relationship between Prostate cancer, Precancer and obesity has been observed in previous studies, however it is unlikely in Indian scenario, but the possibility of its association with cytokines, lipids and androgens level derangement can't be ignored. So, the study is planned to observe the association of metabolic outline, lipid and cytokines profiling, androgens, insulin in Precancer and in Prostate cancer risk and aggressiveness.*

Material and Method: *A cross-sectional study was conducted to observe the association of association of metabolic profile, lipid profile and levels of cytokines, androgens, insulin in PIN and PCa patients. 50 patients of PIN and 50 patients clinically proved and histologically diagnosed with prostate cancer were evaluated in the study.*

Results: *Association of Lipid profile, androgens levels and cytokines levels are significant in precancer and PCa. Leptin may potentiate the growth of cancer cells, adiponectin appears to have an opposite effect.*

Conclusion: *Adiponectin works as anticancer gene and leptin can potentiate the growth of prostate cancer. Cytokines (eg. leptin), lipids and androgens may serve as prognostic parameters for early detection of prostate cancer. This could lead to better understanding of the PCa and in future may help in improving clinical management of the patients.*

Keywords: *Cytokine, Androgens, Insulin, Precancer, Prostate cancer, Lipid Level, Lipid profile.*

Introduction

Prostate cancer is one of the most common cancers in men and its incidence continues to rise in many countries [1]. Screening for and management of early prostate cancer is one of the most challenging and controversial issues in all of medicine. [1,2] Recent articles are focusing on role of obesity and lipid abnormalities operating at the root of PCa. Currently, there is insufficient evidence to directly indicate specific exercise guidelines to ameliorate Pre-cancer and risk factors in prostate cancer patients in Indian population. The incidence of prostate malignancy is also rising in India. Major contribution in the occurrence and progression of prostate cancer include genetic polymorphisms[3], obesity[4], diet[5], altered hormonal status[6], socioeconomic status[7] and others.

The factors contributing to the aggressiveness of prostate cancer lesions are not fully explored due to which the early detection is also not possible. So, it is very essential to discuss first about the precancer with respect to prostate. It is well established that prostate is hormonally influenced and there is evidence signifying that androgenic influences over a period time encourage the process of prostate carcinogenesis, lipid metabolism anti hormonal abnormalities are fundamental aspect of prostate cancer cell biology.[9] Therefore, they may be a potential target for the prevention of the prostate cancer. A well-defined association with cancer and non-neoplastic condition that is 90% chances to be has developed cancer. Precancer in respect to Prostate is designated as Prostatic intraepithelial neoplasia – PIN (Earliest stages of cancer development). Previously it was graded as PIN-1, PIN-2 and PIN-3. Now cases are grouped into-Low grade PIN and High-grade PIN. [10] PIN is currently preferred term for the process involving prostatic ducts and acini, which has also been described as intra-ductal and ductal- acinar dysplasia.

The relationship between obesity and prostate cancer is currently a passionately debatable topic. There is clustering evidence that high dietary fat intake might be associated with the risk of prostate cancer. Obesity is a rising risk factor for the development of several malignancies. Therefore, obesity associated with high leptin levels should be considered a risk factor in patients with prostate cancer.[28]

Recent literature provides evidence that obesity may promote the development of a more aggressive form of prostate cancer resulting in higher recurrence rates after primary therapy and higher cancer mortality rates. [11, 12] Adipocytokine secreted by fat tissue play a role in the genetic predisposition to type-2 diabetes, obesity and insulin resistance. Adiponectin and leptin adipocyte secrete insulin sensitizer, appear to play an important role not only in glucose and lipid metabolism but also in the development and progression of several obesity-related

malignancies.[10] Studies in western countries have shown that PCa is associated with obesity. Relationship between Prostate cancer, Precancer and obesity has been observed in previous studies, however it is unlikely in Indian scenario, but the possibility of its association with cytokines, lipids and androgens level derangement can't be ignored. So, the study is planned to observe the association of metabolic profile, lipid profile, levels of cytokines, androgens, and insulin in Precancer with prostate cancer risk and aggressiveness including genetic biomarkers have several advantages over clinicopathologic indicators in future.

Material and Methods

A cross-sectional study was conducted to observe the association of metabolic profile, lipid profile and levels of cytokines, androgens, insulin in Precancer and in PCa patients. 50 men histologically diagnosed with prostate cancer and 50 men diagnosed with PIN, were evaluated and the following assessments were done.

Anthropometric assessment

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. Body mass index is calculated by weight (in kg)/height^2 (in meter).

Inclusion criteria

Cases were 100 males under the age of 80 (range, 50–80 years), newly diagnosed with histologically confirmed of the prostate cancer at our institution. Patients are willing to participate and willing to give informed consent form

Exclusion Criteria

Men with diabetes mellitus, chronic liver and kidney diseases, heart disease and those taking lipid-lowering drugs and 5-alpha reductase inhibitors were excluded.

Blood sampling, Hormonal and Biochemical Assessment

All men underwent physical examination to measure the height, weight and body mass index (BMI). Peripheral venous blood samples were

withdrawn and collected after an overnight fast at the morning of the day of surgery between 6:00 AM and 8:00 AM and centrifuged for 20 minutes at 2000 rpm. Serum was separated, aliquoted and kept frozen at -80ºC for analysis. Serum adiponectin, leptin, androgens and insulin were measured using commercial ELISA kit (Linco Research, St. Charles, Missouri, USA).

Urologic Data

Digital Rectal Examination (DRE), USG findings, Abdominal/ TRUS and Uroflow parameters. Diagnosis of patients as decided by first line treatment-PSA (Prostate specific antigen) + TRUS (Trans Rectal Ultrasonography) + DRE (Digital Rectal Examination).

Statistical Analysis

Statistical analysis was performed using SPSS version 25.0 The results were presented in mean $\pm$ SD and median. The unpaired t-test for normally distributed variables was used to compare the differences between PIN and PCa patients. The p value <0.05 was considered as significant.

Results

Obesity has long been associated with increased risk of prostate cancer, although studies have been inconsistent. Body mass index (BMI) may not fully reflect the disease related dimensions of obesity since it does not differentiate muscle mass from fat mass. Keeping in mind that central obesity is more common in Indian subcontinent and is associated with metabolic alterations in the body; which is best diagnosed by measuring the WHR correlates much stronger with hormonal and metabolic alterations in comparison to BMI (p value=0.02). On hand plasma adiponectin levels are significantly higher in patients with PCa than PIN, while leptin may potentiate the growth of cancer cells, adiponectin appears to have an opposite effect. Lipid indices, insulin and androgen levels are also shows the positive significant relation with PCa in comparison to Pre-cancer.

Table 1: Distribution of Metabolic Profile

S.No.	Name of Test	Precancer (n=50) Mean $\pm$ SD	PCa (n=50) Mean $\pm$ SD	p value
1.	AGE	65.63 $\pm$ 11.13	64.12 $\pm$ 10.03	0.31
2.	BMI	23.83 $\pm$ 6.62	25.71 $\pm$ 5.47	0.89
3.	WHR	0.95 $\pm$ 0.16	0.79 $\pm$ 0.04	**0.02***

Table 2: Lipid profile and Cytokines level

S. No.	Name of Test	Precancer (n=50) Mean $\pm$ SD	PCa (n=50) Mean $\pm$ SD	p value
1.	Cholesterol(mg/dl)	152.61 $\pm$ 37.43	189.21 $\pm$ 43.87	0.0001
2.	Triglyceride(mg/dl)	112.63 $\pm$ 21.65	134.32 $\pm$ 31.54	0.0001
3.	HDL(mg/dl)	31.24 $\pm$ 8.83	43.72 $\pm$ 9.76	0.0001
4.	LDL(mg/dl)	98.85 $\pm$ 24.27	118.65 $\pm$ 27.81	0.047
5.	VLDL	22.52 $\pm$ 4.33	26.84 $\pm$ 6.30	0.001
6.	Leptin	8.3 $\pm$0.91	136.54 $\pm$29.68	**0.001***
7.	Adiponectin (μg / mL)	12.42 $\pm$3.9	19.83 $\pm$6.34	**0.001***

Table 3: Androgenic parameters and Insulin levels

S.No.	Name of Test	Precancer (n=50) Mean $\pm$ SD	PCa (n=50) Mean $\pm$ SD	p value
1.	T-Testosterone (ng/ml)	6.50 $\pm$ 1.74	4.83 $\pm$ 0.52	0.01
2.	F-Testosterone (pg/ml)	5.4$\pm$0.54	8.7$\pm$1.43	0.001
3.	Insulin (μIu/ml)	11.74 $\pm$ 4.52	19.46 $\pm$ 5.62	0.092

Discussion

The present study was carried out in the Department of Uro Surgery and Pathology, CSM Medical University, Lucknow on 50 patients of PIN and 50 patients of PCa. Prostate cancer is the most common non-skin cancer among men in most western populations, and it is the second leading cause of cancer death among U.S. men. Increasing mortality rate due to this cancer has been observed worldwide. In early stages patients, usually do not experience symptoms and are unlikely to seek medical help until the disease has progressed. Thus, prostate cancer is a key health issues and research is nonstop to weigh up the markers for early detection. So, there is urgent need of clinical indicators for the early detection of PCa.

To date, few studies have investigated the relationship between obesity and prostate cancer and even fewer in Indian men. Amling et al (*2004*)[11] and Freedland (*2004*)[12] et al reported obesity as being associated with higher grade tumors and higher rates of disease recurrence (defined by biochemical relapse-free survival) after treatment with radical prostatectomy using a community and academic based registry with 2,131 radical prostatectomy patients (6.6% African-American), Bassett et al[13] found an association of obesity compared with moderately obese to nonobese men.

WHR is more efficient predictor of mortality in older people[14] waist circumference or body mass index[15] used to assess abdominal obesity or the presence of excess fat in the abdomen. A study on Chinese men (Hsing et al, 2001), it was found that men with a higher waist-hip ratio (WHR) had higher prostate cancer risk with a statistically significantly elevated risk of prostate cancer (p<0.001). Men in the highest tertile of WHR (>0.900) had 8.55 times (95% CI = 2.80 to 26.10) higher risk of prostate cancer than those in the lowest tertile of WHR (<0.873). Similarly, Baltimore study group reported high risk of prostate carcinoma in obese patients for the second through fourth quartiles of the WHR compared with the lowest quartile, however, the risk was not related to waist circumference and BMI. In our study WHR had statistically significant higher values in PIN (0.95 ± 0.16) than that PCa patients (0.89 ± 0.04, p= 0.02), same as WHR seems more significant in higher stage and grade than lower grade patients.

In our study, obese men with prostate carcinoma independent of diabetes had insignificant FBG values in PIN than PCa patients, same relationship are observed in high grade and high stage patients. Mounting evidence has suggested that obesity is associated with lower PSA values,[16,17,18,19,20,21] possibly related to hemodilution from the large plasma volume in obese men.[22] The current study, albeit in a select population of obese men with carcinoma prostate, had statistically significant lower PSA values. In our study, we found the association between adiponectin, leptin levels in PIN and PCa patients. As per in Indian study **Tewari et al (2013)**[23] discussed the how obesity parameters and cytokines levels correlated in high grade and high stage PCa patients, but in this study cytokines are measured in pre-cancer and PCa patients and observed that Adiponectin levels are significantly lower in PIN (11.36 ± 6.7, p = 0.001) than that PCA patients (18.62 ± 22.87). Similar findings were also found in some epidemiological studies that investigated the association between adiponectin and risk of BPH.[24,25] Both adiponectin and leptin had been suggested as potential biological links between obesity and prostate cancer, but few epidemiological data are available regarding their roles in fatal prostate cancer.[26,27]

Studies have suggested that testosterone may exert a differentiating effect on prostate cancer and decreased serum testosterone and increased estradiol levels may be associated with more advanced and poorly differentiated prostate cancer. Lower testosterone levels may also be due to insulin resistance leading to decreased testosterone production by Leydig cells or due to negative feedback effect of inhibitory proteins present in patients with prostate cancer on

hypothalamic-pituitary gonadal axis. In our study, there was a trend of decreased testosterone levels in PCa patients. In the present study, the free testosterone was significantly ($p<0.01$) higher in PCa patients as compared to Precancer patients (Median=3.32). Similarly, the total testosterone was significantly ($p<0.001$) higher in PCa patients (Median=8.66) as compared to Precancer patients. The insulin level was significantly ($p=0.04$) higher in PCa patients as compared to Precancer patients.

Abnormal lipid metabolism can lead to prostatism and dyslipidemia- characterized by high triglyceride and low HDL cholesterol, particularly low HDL-cholesterol is a risk factor in the development of PCa. In the present study, total cholesterol and LDL-cholesterol was significantly higher and HDL-cholesterol was significantly lower in PCa cases compared to PIN. The relationship between insulin level and risk group in prostate cancer, so insulin may be a growth factor. Further studies may document whether serum insulin level might be a independent positive biomarker of prostate cancer aggressiveness.

Conclusion

It is clear that obesity may affect prostate health and could increase the chances of developing PIN to prostate cancer in complex with other predisposing factors, such genetic predisposition in the family. Whether control of obesity and alteration of cytokines, on diagnosis of CaP and BPH, can alter the natural history of the disease remains to be determined. WHR is used to assess abdominal obesity or the presence of excess fat in the abdomen and has been found to be a more efficient predictor of mortality in older people waist circumference or body mass index. Adiponectin works as anticancer gene, on another hand leptin can potentiate the growth of prostate cancer. So, Adiponectin may work as a predictor marker as early stages (PIN). The recent surge in interest in growing prostate cancer, cytokines and obesity will hopefully lead to future studies that

can further clarify the relationship in these increasingly prevalent health problems, larger sample size is needed to establish its association.

Limitations

The genetic and environmental factors affecting men of Indian population cannot be ignored; cross sectional study design and small sample size were drawbacks of our study.

Future Vision

Reduction of obesity and alteration of dietary habits after the diagnosis of prostate cancer and Precancer can alter the natural history of the disease remains to be determined. So, future studies with a larger sample size are needed to establish its association. The recent surge in interest in prostate cancer and obesity will hopefully lead to future studies that can further clarify the relationship between these two increasingly prevalent health problems. Including the genetic biomarkers and genetic polymorphism can lead the better results in future.

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