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Relationship of dyslipidemia, insulin resistance, and prostate-specific antigen with prostate cancer

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Abstract:

Background and Objective: The incidence of prostate cancer is increasing day by day worldwide. Prostate cancer in India is the 10th most common malignancy affecting men although its incidence is rising in India. This study is designed to the effect of dyslipidemia, altered serum glucose, insulin resistance, and prostate-specific antigen (PSA) on the risk of prostate cancer. **Materials and Methods:** The study was conducted on a total of 150 patients, in which 75 patients were of prostate cancer considered as cases and 75 were healthy individuals as controls. About 8 ml of blood samples was drawn to determine fasting glucose, lipid profile, serum insulin, and serum PSA. Serum glucose, total cholesterol, high-density lipoprotein cholesterol (HDL-C), and triglyceride (TG) were measured using enzymatic kits of auto analyzer. Very low-density lipoprotein-C (VLDL-C) and LDL-C were calculated by Friedwald's formula. Serum insulin and serum PSA were estimated by immunoenzymatic assay. Body mass index (BMI) was calculated as "weight in kilograms divided by height in meters squared (kg/m^2)". Insulin resistance was assessed by homeostasis model assessment insulin resistance index (HOMA-IR) and calculated as follows: "fasting glucose (mg/dL) × fasting insulin (mU/mL)/405". Blood pressure was measured in the sitting position after a 10 min resting period. **Observation and Results:** Clinical variables such as age, BMI, blood pressure, lipid profile, serum glucose, serum insulin, HOMA-IR, and serum PSA in case and control groups were compared using the unpaired Student's *t*-test. We found that BMI and the level of serum glucose, serum insulin, HOMA-IR, and serum PSA were significantly increased in prostate cancer patients as compared to control. In prostate cancer patients, HDL-C significantly decreased ($P < 0.001$) while total cholesterol, TG, LDL-C, and VLDL-C were significantly increased ($P < 0.001$) as compared to control group. **Conclusion:** This study has shown significant association of high BMI, dyslipidemia, insulin resistance, and PSA with prostate cancer.

Key words:

Body mass index, dyslipidemia, insulin resistance, prostate cancer, prostate-specific antigen

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Introduction

Data obtained from the International Agency for Cancer Research suggest low incidence of prostate cancer in East Asian countries in comparison to the western countries.[1] Prostate cancer in India is the 10th most common malignancy affecting men although its incidence is rising in India. The reasons for this racial disparity are uncertain. Emerging literature has implicated that obesity and diet,[2,3] hypertension, dyslipidemia, disturbed glucose metabolism, insulin resistance, socioeconomic status, and changes in lifestyle because of Westernization are potential risk factors for progression of prostate cancer.[4-9] Obesity suggests higher stores of adipose tissue as a source of cholesterol and triglycerides (TGs);[10] therefore, a disturbed lipid profile may be seen in the patients of prostate cancer. While a high-fat diet has been associated with a higher incidence of prostate cancer, findings from epidemiological studies examining the link between prostate cancer and obesity have not been consistent.[11] The oxidative stress generated by hyperglycemia increases reactive oxygen species, which leads to the activation of various redox-sensitive cell signaling molecules and the production of cytotoxic materials.[12] Further, many studies have shown an association of dyslipidemia in prostate cancer.[13]

Elevated serum glucose leads to rapid increment of insulin from the pancreatic beta cells, and high insulin levels can be associated with insulin resistance. In addition, insulin has potent mitogenic and growth-stimulatory effects on the prostate and other tissues, and alterations in these effects

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could potentially contribute to the development of malignancy.[14] Therefore, among the physiopathological entities that comprise metabolic syndrome, serum glucose, serum insulin, and insulin resistance may link to the risk of prostate cancer. The present case–control study was designed to compare the body mass index (BMI), hypertension (systolic blood pressure [SBP] and diastolic blood pressure [DBP]), lipid profile, serum glucose, serum insulin, HOMA-IR, and serum prostate-specific antigen (PSA) between prostate cancer patients and healthy individuals.

Materials and Methods

Study population

The case–control study was conducted on a total of 150 patients, of which 75 cases were with newly diagnosed prostate cancer and 75 controls were among age-matched healthy individuals. Cases recruited were 50–80-year-old males with histologically confirmed primary adenocarcinoma of the prostate at our institution between 2013 and 2015. Age-matched disease-free individuals, without any complication, were selected as controls.

Specimen and laboratory assays

About 8 ml of blood sample was withdrawn from the antecubital vein following overnight fasting. The blood sample was collected in plain vacutainers. Serum was separated from the clotted blood by centrifugation for 15 min at 3000 rpm at room temperature. All serum samples were stored at −80°C until use. Serum glucose level was estimated by glucose oxidase and peroxidase method. Serum total cholesterol (normal value 150–200 mg/dl), high-density lipoprotein cholesterol (HDL-C; normal values 35–70 mg/dl), and TG (normal values 60–170 mg/dl) were measured using commercially available kit of auto analyzer. Very low-density lipoprotein (VLDL-C) and LDL-C (normal value 12-34 mg/dl) were calculated by Friedwald's formula. All biochemical investigations were done by fully automated analyzer Turbo cam 100 (CPC diagnostics Pvt. Ltd, Alwerpet, Chennai, India). The Serum Insulin (normal value <10 μlU/ml) done by ELISA is a solid phase two-site enzyme immunoassay. It is based on the direct sandwich technique and was estimated by Calbiotech, Inc., Insulin ELISA kit and Catalog No. IS130D (96 Tests). The PSA (normal value ≤4 ng/ml) done by ELISA kit is a solid phase assay based on a streptavidin-biotin principle were estimated by Calbiotech, Inc., PSA ELISA kit and Catalog No. PS235T (96 Tests). All assays were performed according to the respective manufacturer's instructions. Insulin resistance was assessed by, homeostasis model assessment insulin resistance index (HOMA-IR) and calculated as: "fasting glucose (mg/dl) × fasting insulin (μlU/ml)/405". BMI was calculated as "weight in kilograms divided by height in meters squared (kg/m^2)". Blood pressure (SBP and DBP) was measured in the sitting position after a 10-min resting period.

Exclusion criteria

The patients were excluded if they suffered from diabetes, chronic liver disease, chronic renal disease, heart disease, and those taking the medication that influence on blood glucose, serum lipid profile, and serum insulin.

Statistical analysis

Metabolic parameters such as age, BMI, SBP, DBP, lipid profile, serum glucose, serum insulin, HOMA-IR, and serum PSA in case and control groups were compared using the Unpaired Student's *t*-test. Pearson correlation analysis was performed to evaluate relationships between PSA and other metabolic parameters.

Statistical analysis was performed using SPSS version 17 (SPSS Inc., 233, South Wacker Drive, Chicago, IL). $P < 0.05$ was considered statistically significant.

Ethics statement

The study was approved by the Ethical Committee of the Institute. Informed consent was obtained from each patient.

Results

Table 1 shows that the mean age of cases was 65.86 years and of the controls was 65.2 years. There was no significant difference in age between the two groups. BMI, SBP, and DBP were significantly higher in the prostate cancer patients compared to controls. Serum glucose, serum insulin, HOMA-IR, and serum PSA level were significantly increased ($P < 0.001$) in prostate cancer patients as compared to controls.

Table 2 shows lipid profiles of the prostate cancer patients and controls. Serum lipid profile (total cholesterol, TG, LDL-C, and VLDL-C) except HDL-C increased significantly ($P < 0.001$) compared to controls. HDL-C significantly decreased ($P < 0.001$) in prostate cancer patients as compared to controls. Some other studies also showed similar results.

Pearson correlation of serum PSA showed highly significant ($P < 0.001$) positive linear relationship with BMI [Figure 1], SBP [Figure 2], LDL-C, [Figure 3] and also showed significant ($P < 0.05$) positive linear relationship with DBP [Figure 4], total cholesterol [Figure 5], serum insulin [Figure 6], and HOMA-IR

Table 1: Comparison of parameters between prostate cancer cases and controls

Parameters	Mean±SD		*P*
	Control (*n*=75)	Case (*n*=75)	
Age (years)	65.2±4.4	65.86±4.38	NS
BMI (kg/m^2)	23.74±1.48	26.39±2.73	<0.05
SBP (mmHg)	120±3.77	131.18±6.96	<0.001
DBP (mmHg)	79.6±3.14	85.96±7.85	<0.001
Fasting glucose (mg/dl)	94.5±6.41	119.9±8	<0.001
Serum insulin (μlU/ml)	9.51±1.84	15.77±4.05	<0.001
HOMA-IR	2.22±0.49	4.71±1.48	<0.001
PSA (ng/ml)	4.27±1.17	25.9±22.8	<0.001

BMI: Body mass index, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, HOMA-IR: Homeostasis model assessment insulin resistance index, PSA: Prostate-specific antigen, NS: Not significant, SD: Standard deviation

Table 2: Lipid profile comparison between prostate cancer cases and controls

Parameters	Mean±SD		*P*
	Control (*n*=75)	Case (*n*=75)	
Total cholesterol (mg/dl)	165.6±16.13	229.9±35.2	<0.001
HDL-cholesterol (mg/dl)	46.7±5.93	32.8±5.37	<0.001
LDL-cholesterol (mg/dl)	90.2±18.2	158.9±34	<0.001
Triglycerides (mg/dl)	143.2±40.3	190.6±37.3	<0.001
VLDL-cholesterol (mg/dl)	28.6±8.06	38.13±7.46	<0.001

SD: Standard deviation, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, VLDL: Very low-density lipoprotein

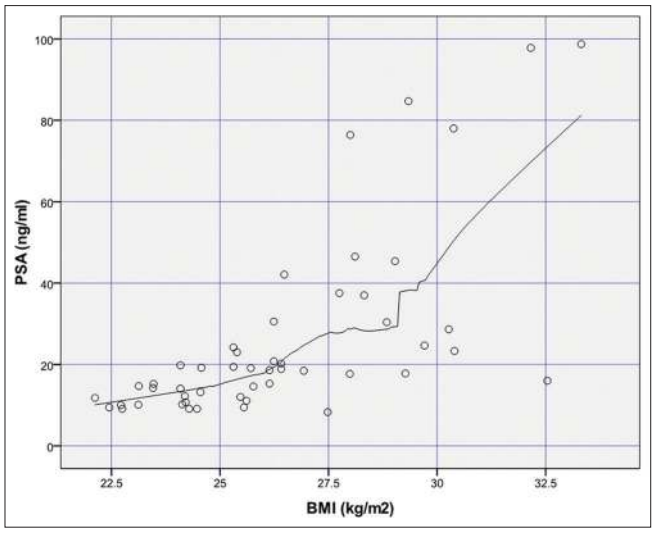

Figure 1: Positive Pearson correlation between serum prostate-specific antigen and body mass index

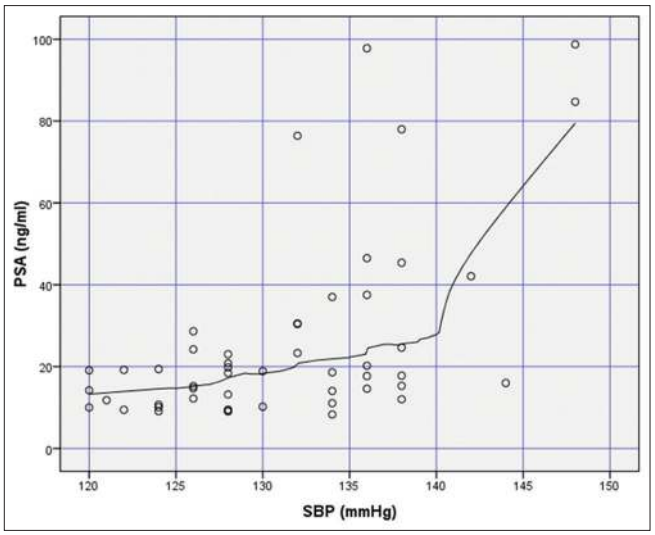

Figure 2: Positive Pearson correlation between serum prostate-specific antigen and systolic blood pressure

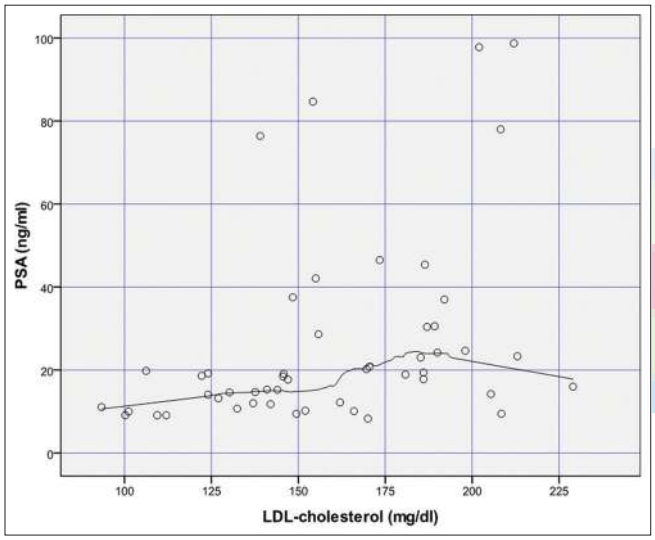

Figure 3: Positive Pearson correlation between serum prostate-specific antigen and low-density lipoprotein cholesterol

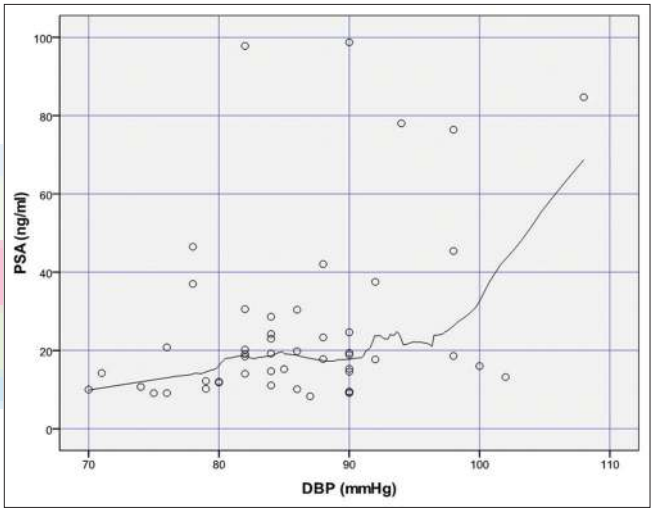

Figure 4: Positive Pearson correlation between serum prostate-specific antigen and systolic-diastolic blood pressure

[Figure 7]. Serum PSA significantly ($P < 0.001$) negatively correlate with HDL-C [Figure 8] and no significantly correlate with age, fasting glucose, TG, and VLDL-C [Table 3].

Discussion

We examined the relationship between serum PSA and dyslipidemia, hyperinsulinemia. We observed significantly high levels of BMI, serum glucose, total cholesterol, TG, LDL-C, VLDL-C, serum insulin, HOMA-IR, and serum PSA in prostate cancer patients in comparison to controls, suggesting a significant correlation between serum PSA and BMI, SBP, DBP, total cholesterol, LDL-C, serum insulin, and HOMA-IR in prostate cancer. Age of the patients was almost similar in both case (65.86 ± 4.38 years) and control (65.2 ± 4.4 years) groups.

The current study reveals that fasting glucose, insulin resistance, and lipid profile are associated with prostate cancer susceptibility and clinicopathological characteristics. Serum glucose is directly controlled by insulin, and thus higher glucose level induces insulin secretion from pancreatic beta cells. Such a hyperinsulinemia is associated with insulin resistance and, therefore, contributes to the pathogenesis of type 2 diabetes. The role of insulin in cancer has been studied, and high level of circulating insulin decreases the production of insulin-like growth factor I (IGF-I)-binding proteins and increases the levels of free IGF-I, which promotes carcinogenesis.[15] Insulin is known to be a direct mitogen for *in vitro* prostate growth and is necessary for the growth of prostate cancer cells in culture.[16]

In the present study, serum glucose, insulin, and HOMA-IR showed the consistent results in terms of the prostate cancer risk. Higher glucose and higher insulin were positively related to the susceptibility to the risk of prostate cancer. Reports of the insulin resistance in relation to prostate cancer risk have been conflicting. Hsing *et al*. conducted a population-based case–control study including 128 cases and 306 controls in China

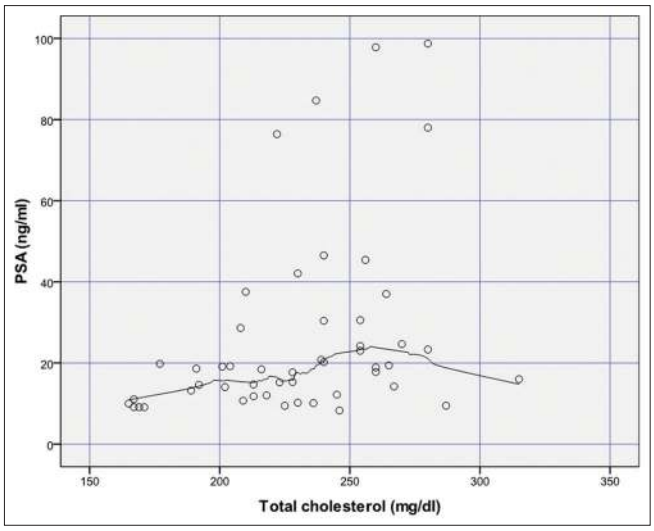

Figure 5: Positive Pearson correlation between serum prostate-specific antigen and total cholesterol

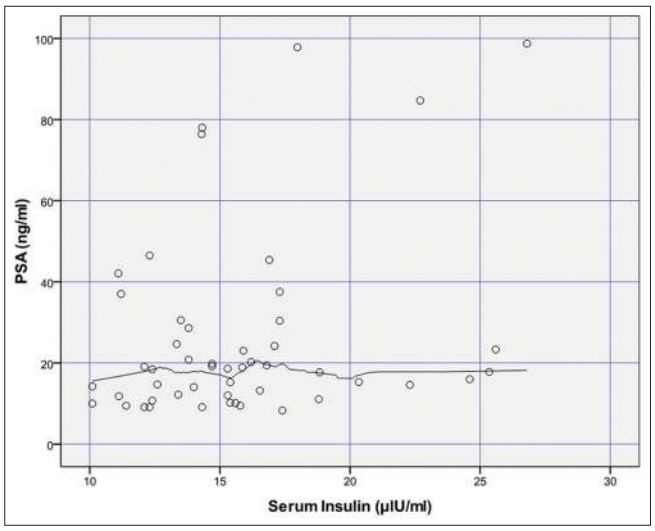

Figure 6: Positive Pearson correlation between serum prostate-specific antigen and serum insulin

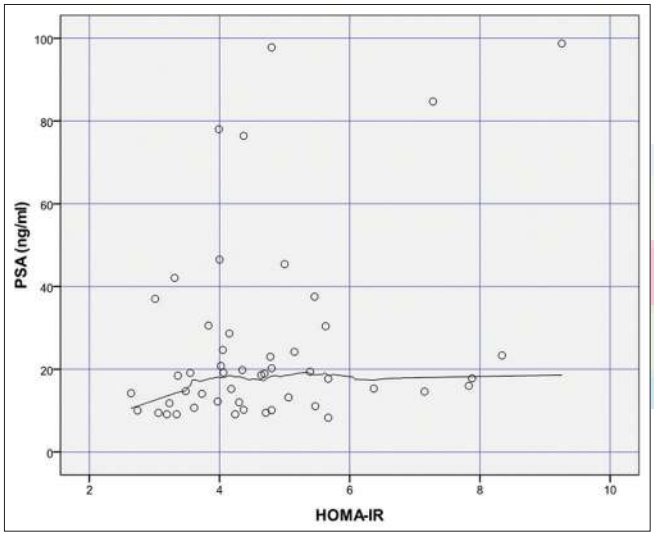

Figure 7: Positive Pearson correlation between serum prostate-specific antigen and homeostasis model assessment insulin resistance index

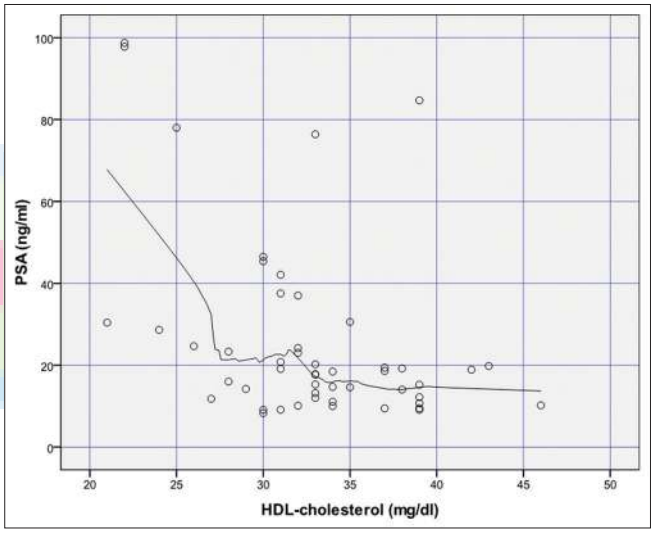

Figure 8: Negative Pearson correlation between serum prostate-specific antigen and high-density lipoprotein cholesterol

and concluded that insulin resistance was associated with a higher risk of prostate cancer among Chinese men.[17] Albanes *et al*.[18] performed a prospective cohort study with 100 cases and 400 controls and reported that increased HOMA-IR was associated with the significantly increased risks of prostate cancer. In contrast to previous studies, however, Stocks *et al*. reported that HOMA-IR was strongly inversely related to overall prostate cancer risk, especially among young men and among men with nonaggressive disease through a prospective cohort in Northern Sweden with 392 cases and 392 matched controls.[19] Lehrer *et al*. showed higher insulin levels ($P = 0.033$) to be present in patients with high-risk prostate cancer, which was defined as Gleason score >7, tumor in seminal vesicle on biopsy, PSA >15, or stage T2c or T3.[20] In the present study, increased HOMA-IR was associated with the significantly increased risks of prostate cancer.

There is a gathering body of research to explore the interrelationship between lipid and cancer, particularly prostate cancer development and progression. According to one north Indian study, central obesity, dyslipidemia, and hyperinsulinemia could be associated with high-grade prostate cancer.[21] In one study, rats fed with cholesterol-rich diet exhibited both altered blood lipid profiles and hyperplastic changes in the prostate.[22,23] There is also evidence from *in vitro* studies that prostate cancer cells migrate to adipocytes within red bone marrow where metastases are very common and an experiment showed that attractiveness of human bone marrow to prostate cancer cells decreased when bone marrow stroma was depleted of lipid cells.[24,25] It has been shown that prostate cancer cells take up lipid directly as a source of energy for the process of tumor maintenance, proliferation, and migration.[26] A report by Platz *et al*. showed that there was a 50% reduction in mortality due to prostate cancer in men taking statins, which are lipid-lowering drugs.[27] A positive correlation was also found between serum TGs and prostate cancer with an odds ratio (OR) of 1.148 (95% confidence interval [CI]:

Table 3: Pearson correlation coefficient (*r*) between serum prostate-specific antigen and various metabolic parameters among prostate cancer patients

Parameters	*r*	*P*
Age (years)	0.04	NS
BMI (kg/m2)	0.68**	<0.001
SBP (mmHg)	0.56**	<0.001
DBP (mmHg)	0.35*	<0.05
Fasting glucose (mg/dl)	0.24	NS
Total cholesterol (mg/dl)	0.35*	<0.05
HDL-cholesterol (mg/dl)	−0.42**	<0.001
LDL-cholesterol (mg/dl)	0.38**	<0.001
Triglycerides (mg/dl)	0.22	NS
VLDL-cholesterol (mg/dl)	0.22	NS
Serum insulin (μlU/ml)	0.28*	<0.05
HOMA-IR	0.29*	<0.05

*Significant at the 0.05 level, **Correlation is significant at 0.01. BMI: Body mass index, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, HOMA-IR: Homeostasis model assessment insulin resistance index, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, VLDL: Very low-density lipoprotein, NS: Not significant

1.003–1.315; $P < 0.05$) after correcting for age, BMI, diabetes, and comedication with statin.[28] Platz *et al*. reported that men with low cholesterol <200 mg/dL had a lower risk of Gleason 8–10 prostate cancer (OR: 0.41; 95% CI: 0.22–0.77) than men with high cholesterol (≥200 mg/dL).[29,30] *In vitro* studies suggested a definite relationship of lipids with prostate cell metabolism, which is also strengthened by correlation studies on human prostate cancer patients. Meta-analysis could unveil the relationship more clearly; however, that has to wait generation of more data on a larger pool of samples. Therefore, more *in vivo* studies are required to understand the level of correlation between lipid profile and prostate cancer.[30,31]

Conclusion

Our study suggests that dyslipidemia and disturbed glucose metabolism are correlated with prostate cancer in Indian males. It also indicates that dyslipidemia and hyperinsulinemia in obese patients, independent of diabetes, are involved in the pathogenesis of prostate carcinoma and raises the potential that control of obesity in these men or targeted treatment strategies may provide a means of reducing poor outcome in this high-risk group. Our study has particularly put forth significant differences in metabolic indices and lipid profile between prostate cancer and controls. Among biochemical parameters, serum glucose, total cholesterol, TG, LDL-C, VLDL-C, serum insulin, HOMA-IR, and serum PSA are significantly elevated in patients of prostate cancer in comparison to controls, suggesting a significant positive correlation between serum PSA and total cholesterol, LDL-C, serum insulin, and insulin resistance in prostate cancer. Serum HDL-C significantly decreased in prostate cancer patients as compared to control and showed a significant negative correlation between serum PSA and HDL-C.

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Nil.

Conflicts of interest
There are no conflicts of interest.

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