RESEARCH ARTICLE

Significant Association of Metabolic Indices, Lipid Profile, and Androgen Levels with Prostate Cancer

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Abstract

Objectives: To compare the metabolic indices, lipid profile, androgens, and prostate specific antigen between prostate cancer and BPH and between grades of prostate cancer in a cross-sectional study. Materials and Methods: The study enrolled 95 cases of prostate cancer and 95 cases of benign prostatic hyperplasia (BPH). Prostate gland volume was measured using transrectal ultrasound. We compared insulin, testosterone, dihydrotestosterone, prostate specific antigen levels and lipid profile between prostate cancer of different grades and BPH. Further, prostate cancer patients were classified into low grade and high grade. Unpaired t-test for normally distributed variables and Man-Whitney U test for non-normal variables were used to assess differences. Results: We found that prostate cancer patients had significantly higher levels of insulin, testosterone, PSA, cholesterol, triglycerides, low-density lipoprotein (LDL) and very low-density lipoprotein (VLDL) in comparison to their BPH counterparts. Higher levels of these parameters also correlated with a higher grade of the disease. Conclusions: We conclude that higher levels of insulin, testosterone, PSA, and cholesterol correlate with a higher risk of prostate cancer, and also with a higher grade of the disease.

Keywords: Prostate cancer - BPH - lipid profile - testosterone - dihydrotestosterone - PSA

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Introduction

Data obtained from the International Agency for Cancer Research (IARC) suggests low incidence of prostate cancer in East Asian countries in comparison to the western countries (Center et al., 2012). Prostate cancer in India is the 10th most common malignancy affecting men, although its incidence is rising in India as well. The reasons for this racial disparity are uncertain. A deeper research into the factors that differ significantly across these continents may answer the questions regarding its incidence and causative factors. The foremost risk factors that may underlie these regional/ethnic differences could be endocrine variations, genetic polymorphisms (Zeigler-Johnson et al., 2002) altered hormonal status (Garfinkel, 1986), socioeconomic status (Nomura and Kolonel, 1991) and obesity and diet (Stephen and Brady, 2005; Girling et al., 2007) Diet, disturbed glucose metabolism, and metabolic syndrome are extremely interesting factors for in depth exploration in relation to the risk of prostate cancer (Long et al., 2012; McGrowder et al., 2012; Tewari et al., 2012; Ozbek et al., 2014, Pandeya et al. 2014) In an earlier study, we presented that body mass index and waist to hip ratio were significantly higher in prostate cancer in comparison to BPH and so in high grade prostate cancer in comparison to low grade cancer (Tewari et al., 2013).

Obesity suggests higher stores of adipose tissue as a source of cholesterol and triglycerides (Tewari et al., 2011); therefore, a disturbed lipid profile may be seen in the patients of prostate cancer and BPH. 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 (Hsing et al., 2007). Further, many studies have shown an association of dyslipedimia in BPH (Nandeesha et al., 2006) and prostate cancer (Gillitizer et al., 2005; Clarke and Brown, 2007). Distrubed level of adipocytokines has been correlated with PCa risk and its higher grade by us (Tewari et al. 2013) and others (Zhang et al., 2014). It has been established that Dihydrotestosterone is the principal androgen responsible for both normal and hyperplastic growth of the prostate gland. Suppression of DHT synthesis may inhibit carcinogenic transformation (Brawley, 2003). The role of the testosterone in the initiation of PCa has been debated (Dandona et al., 1998). We undertook the present study to further extend the analysis so as to understand the differences in the metabolic indices, insulin, testosterone,

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dihydrotestosterone, and lipid profile between prostate cancer and BPH and between high and low grade prostate cancer.

Materials and Methods

The details of patient recruitment and clinical parameters are given in our earlier study (Tewari et al., 2013). Apart from the clinical measures presented in the above-mentioned study, we undertook assays to measure the levels of insulin, testosterone, dihydrotestosterone, and detailed lipid profile. For hormonal assessment, peripheral venous blood samples were withdrawn and collected after an overnight fast in the morning of the day of surgery between 6:00 and 8:00 AM. Serum was separated, aliquoted and kept frozen at -80ºC for further evaluations. Serum prostate specific antigen (PSA normal value ≤4ng/ml), testosterone, DHT, insulin levels, high-density lipoprotein (HDL; normal values 35-70mg/dl), triglycerides (TG; normal values 60-170mg/dl), cholesterol (normal value 150-200mg/dl), and low-density lipoprotein (LDL; normal value 12-34mg/dl) were measured using semi auto analyzer.

Staging and Grading: Resected prostate specimen were fixed in 10% buffered formalin and processed for histopathological examination as per standard histology protocol. Briefly, 3-5 micron thick sections were cut and stained with haematoxylin and eosin. The histological diagnosis of BPH and PCa was done by expert histopathologists. For further details, please see our earlier study (Tewari et al., 2011).

Statistics: Unpaired t-test for normally distributed variables and Man-Whitney U test for non-normal variables were used to compare the differences between PCa and BPH groups and between low and high-grade PCa groups. The p value <0.05 was considered to be statistically significant.

Results

Insulin level was significantly (p=0.04) higher in the PCa group (Median=15.60) in comparison to the BPH group (Median=14.91). Similarly, insulin level in the high grade PCa group (Median=16.75) was significantly higher (p<0.0001) in comparison to that of low grade PCa group

Table 1. Comparison of Parameters between BPH and PCa Patients

	BPH (n=95) Mean±sd	PCa (n=95) Mean±sd	p-value*
Anthropometric measurements			
Age	65.66±10.66	66.54±7.11	0.51
BMI	22.15±2.90	26.58±4.76	<0.001**
WHR	0.86±0.15	1.08±0.37	<0.0001**
Insulin & Insulin Resistance			
Insulin	14.91±11.23 -14.91	16.00±5.13 -15.6	0.04**
IR	65.55±48.84 -53.33	68.54±29.37 -64.89	0.01**
Androgen			
Free testosterone	3.78±2.99 -3.32	6.82±4.42 -6.67	<0.0001**
Total testosterone	5.67±3.14 -5.22	8.60±4.74 -8.66	<0.0001**
Dihydrotestosterone	575.32±202.42 -535.71	8.51±5.44 -7.6	<0.0001**
Prostate-Specific Antigen			
Free PSA	1.73±2.58 -1.14	59.92±42.81 -46.7	<0.0001**
Total PSA	5.85±3.65 -5.6	61.01±44.01 -49.5	<0.0001**
Blood Pressure			
Systolic	129.42±12.56	129.58±15.66	0.94
Diastolic	91.71±18.03	85.73±13.44	0.01**
Lipid Profile			
Total cholesterol	122.48±23.31	148.42±23.37	<0.0001*
HDL	30.29±6.95	32.02±6.71	0.08
Total cholesterol/HDL	4.24±1.19	4.85±1.30	0.001*
TG	111.99±22.30	165.79±31.52	<0.0001*
LDL	61.96±19.81	64.14±27.57	0.53
VLDL	23.10±11.00	31.66±7.68	<0.0001*
Fasting blood glucose	102.68±24.43	106.41±19.16	0.24
Comparison of Prostate Volume			
Prostate volume	32.83±11.57 -32	31.57±7.43 -32	0.67

Table 2. Comparison of Parameters between Low Grade and High Grade Patients

	Low grade (n=33) Mean±sd (Median)	High grade (n=62) Mean±sd (Median)	p-value*	Unadjusted OR (95%CI)
Anthropometric parameters				
Age	66.58±7.28	66.52±7.08	0.97	0.99 (0.94-1.06)
BMI	24.82±3.67	27.52±5.03	0.008**	1.14 (1.03-1.16)
WHR	0.97±0.29	1.14±0.39	0.03**	4.32 (1.08-17.33)
Insulin and Insulin Resistance				
Insulin	13.18±3.69 -12.1	17.50±5.18 -16.75	<0.0001**	1.28 (1.12-1.46)
IR	50.97±17.66 -45.86	77.89±30.17 -73.1	<0.0001**	1.06 (1.03-1.09)
Androgen				
Free testosterone	9.73±4.36 -10.51	5.27±3.62 -4.95	<0.0001**	0.76 (0.67-0.86)
Total testosterone	11.62±4.61 -12.5	7.00±4.00 -6.94	<0.0001**	0.78 (0.67-0.88)
Dihydrotestosterone	6.37±2.33 -6.6	9.66±6.24 -8.67	0.02**	1.17 (1.04-1.32)
Prostate volume in higher Grade of Prostate Cancer patients				
Prostate volume	26.87±7.02 -23	35.31±7.24 -33.5	<0.0001*	1.20 (1.10-1.30)

Table 3. Comparison of Parameters between Stage III and Stage IV Patients

	Stage III (n=64) Mean ± sd (Median)	Stage IV (n=31) Mean ± sd (Median)	p-value*	Unadjusted OR (95%CI)
Anthropometric parameters				
Age	66.66±7.53	66.29±6.28	0.82	0.99 (0.93-1.06)
BMI	27.15±4.44	25.42±5.30	0.1	0.92 (0.84-1.02)
WHR	0.93±0.20	1.39±0.44	<0.0001**	3.74 (2.68-15.67)
Insulin level				
Insulin	15.44±5.16 -14.55	17.16±4.95 -16.8	0.05	1.07 (0.98-1.16)
IR	64.07±24.58 -63.6	77.76±36.12 -72.2	0.08	1.02 (1.00-1.03)
Androgen				
Free testosterone	7.25±4.71 -7.06	5.94±3.67 -5.59	0.17	0.93 (0.84-1.03)
Total testosterone	9.03±5.03 -9.05	7.71±4.04 -7.58	0.17	0.94 (0.86-1.03)
Dihydrotestosterone	8.63±5.16 -7.8	8.28±6.06 -6.7	0.51	0.99 (0.91-1.07)
PSA				
Free PSA	29.03±16.01 -22.35	112.86±24.95 -120	<0.0001*	1.67 (1.01-2.77)
Total PSA	34.13±18.32 -33.8	116.51±25.28 -126.8	<0.0001*	1.69 (1.02-2.79)
Prostate volume in higher Stage of Prostate Cancer patients				
Prostate volume	32.76±8.82 -32.5	31.58±6.78 -32	0.63	0.98 (0.93-1.04)

Table 4. Level of Various Biochemical Parameters Adjusted for BMI and WHR in Different Groups

Parameters	BPH *vs* PCa		Grade Low *vs* High		Stage-III *vs* IV	
	OR (95%CI)	R^2, p-value	OR (95%CI)	R^2, p-value	OR (95%CI)	R^2, p-value
Adiponectin	1.1 (1.06-1.15)	0.70, <0.0001*	0.86 (0.80-0.93)	0.33, <0.0001*	0.96 (0.90-1.02)	0.33, 0.22
Leptin	0.99 (0.99-1.02)	0.36, 0.56	1.36 (1.11-1.67)	0.65, 0.003*	1.09 (0.99-1.02)	0.32, 0.35
IL-6	0.76 (0.69-0.84)	0.63, <0.0001*	1.16 (1.08-1.24)	0.36, <0.0001*	1.03 (0.98-1.08)	0.32, 0.22
Insulin	1.01 (0.97-1.04)	0.36, 0.56	1.27 (1.10-1.47)	0.27, 0.001*	1.05 (0.94-1.16)	0.32, 0.41
IR	1 (0.99-1.01)	0.36, 0.72	1.05 (1.03-1.08)	0.32, <0.0001*	1.02 (0.99-1.04)	0.34, 0.08
Free testosterone	0.77 (0.69-0.86)	0.44, <0.0001*	0.78 (0.69-0.89)	0.29, <0.0001*	0.91 (0.81-1.05)	0.33, 0.21
Total testosterone	0.8 (0.72-0.88)	0.43, <0.0001*	0.79 (0.70-0.90)	0.28 <0.0001*	0.92 (0.81-1.04)	0.33, 0.17
DHT	1.17 (0.68-4.20)	0.75, 0.98	1.22 (1.03-1.39)	0.25, 0.003*	1.07 (0.97-1.18)	0.33, 0.16
Free PSA	0.67 (0.53-0.88)	0.47, <0.0001*	0.78 (0.69-0.89)	0.36 0.002*	1.44 (1.01-1.67)	0.35, 0.02*
Total PSA	0.69 (0.54-0.97)	0.60, <0.0001*	0.77 (0.66-0.89)	0.34 0.001*	1.67 (1.09-1.87)	0.53, <0.0001*
Prostate volume	1.03 (0.99-1.07)	0.36, 0.15	1.19 (1.10-1.30)	0.34, <0.0001*	0.99 (0.92-1.05)	0.32, 0.65

(Median=12.10). This in connection with our previous findings suggested disturbed glucose metabolism in the PCa group in comparison to the BPH group (Tewari R et al., 2011).

Free testosterone was significantly (p<0.0001) higher in the PCa group (Median=6.67) in comparison to the BPH group (Median=3.32). Testosterone level of the patients was significantly lower (p<0.0001) in the high-grade PCa group (Median=4.95) in comparison to the low-grade group (Median=10.51). Similarly, the total testosterone was significantly higher (p<0.0001) in PCa patients (Median=8.66) in comparison to BPH patients (Median=5.22). The total testosterone level was significantly lower (p<0.0001) in the high grade PCa

group (Median=6.94) in comparison to the low-grade PCa group (Median=12.50). However, dihydrotestosterone was significantly lower in PCa patients (Median=7.60) in comparison to the BPH patients (Median=535.71). The DHT level was significantly higher (p=0.02) in the high grade PCa group (Median=8.67) in comparison to the low-grade PCa group (Median=6.60). Therefore, a high level of testosterone correlated with PCa while a high level of DHT correlated with BPH. The free PSA level was significantly higher (p<0.0001) in the PCa group (Median=46.70) in comparison to the BPH group (Median=1.14). Similarly, total PSA was significantly higher (p<0.0001) in PCa patients (Median=49.50) as compared to BPH patients (Median=5.60).

Total cholesterol level was significantly higher (p<0.0001) in PCa (148.42±23.37) patients as compared to BPH patients (122.48±23.31), and a higher cholesterol level was observed in high grade PCa group (148.42±23.3) in comparison to low-grade PCa patients (149±23.4). HDL was insignificantly higher (p=0.08) in PCa patients (32.02±6.71) as compared to BPH patients (30.29±6.95), and an insignificantly higher HDL level was observed in high grade PCa group (32.02±6.01) in comparison to low grade PCa group (30.8±7.8). The triglyceride level was significantly higher (p<0.0001) in PCa (165.79±31.52) patients in comparison to BPH patients (111.99±22.30), but triglyceride level was insignificantly higher in (165.3±27) high grade PCa in comparison to low grade PCa patients (166±38.9). LDL was insignificantly (p>0.05) higher in PCa patients (64.14±27.57) in comparison to BPH patients (61.96±19.81), and LDL level was insignificantly higher in high grade PCa group in comparison to low grade PCa group. The VLDL level was significantly higher (p<0.0001) in PCa patients (31.66±7.68) in comparison to BPH patients (23.10±11.00).

Discussion

We observed significantly high levels of insulin, BMI, WHR, and cholesterol, triglycerides, LDL and VLDL in PCa patients in comparison to BPH and further so in high grade PCa versus low grade PCa, suggesting a significant correlation between disturbed glucose and lipid metabolism with PCa. Obesity has long been associated with increased risk of prostate cancer; however, the results across the studies have been inconsistent (Giovannucci et al., 1997). There are contradictory reports stating either inverse or no correlation between BMI/obesity parameters and BPH or prostate cancer. The relationship between prostate growth/volume and obesity becomes evident from the studies comparing these parameters in BPH patients versus controls. Zucchetto et al observed that overweight was modestly but inversely related to BPH (Zucchetto et al., 2005) and BMI and waist circumference at evaluation were inversely associated with BPH risk. Another study showed no association between anthropometry and several different objective and subjective measures of BPH in 475 men enrolled in the Olmsted County cohort (Burke et al., 2006). Body mass index (BMI) may not fully reflect the disease-related dimensions of obesity since it does not differentiate muscle mass from fat mass. Central obesity, which is best diagnosed by measuring the WHR correlates much stronger with hormonal and metabolic alterations in comparison to BMI. In an earlier case-control study, we showed that high WHR and BMI correlate with PCa and higher grade of the disease (Tewari et al., 2011).

In our study, age of the patients was almost similar in both low grade (66.58±7.28) and high grade (66.52±7.08) groups. We found that high Gleason score was significantly associated with higher WHR, raising the suspicion that central obesity may predispose to high-grade prostate cancer (p<0.001). Except for a few prospective studies, there is less support for the hypothesis that central adiposity (measured as waist circumference or WHR) is a risk factor for prostate cancer. We found that disturbed glucose metabolism and alterations in lipid profile correlate with PCa and with higher grade of the disease. Obesity and dyslipedimia have been associated with an increased risk of BPH (Parsons et al., 2008). According to one north Indian study, central obesity, dyslipedimia, and hyperinsulinemia could be associated with high-grade CaP (Prabhat et al., 2010). In one study, rats fed with cholesterol-rich diet exhibited both altered blood lipid profiles and hyperplastic changes in the prostate (Hammarsten et al., 1998; Mitropoulos et al., 2003). Hammarsten et al found in a cohort of Swedish men with BPH that lower HDL cholesterol, higher LDL cholesterol, and higher triglycerides were associated with increased prostate volume (Hammarsten et al., 1998). While in a case control study, Indian men undergoing BPH surgery were more likely to have lower HDL and higher LDL cholesterol compared to controls (Nandeesha et al., 2006); there was no association of patient-reported hyperlipidemia with histological BPH in a case-control analysis on Italian men (Zucchtto et al., 2005) and no association of serum lipids or lipoproteins with International Prostate Symptom Score or prostate volume in a cohort of Turkish men (Lekili et al., 2006). Similarly, no association of serum lipids or lipoproteins was found with ICD-9 coded BPH diagnosis in a cohort of U.S. Air Force Veterans (Gupta et al., 2006).

There is a gathering body of research to explore the inter-relationship between lipid and cancer, particularly PCa development and progression. It has been shown that prostate cancer cells take up lipid directly as a source of energy for the process of tumor mantainence, proliferation, and migration (Clarke et al., 2009). A report by Platz et al showed that there was a 50% reduction in mortality due to PCa in men taking statins, which are lipid-lowering drugs (Platz et al., 2006). There is also evidence from *in vitro* studies that prostate cancer cells migrate to adipocytes within red bone marrow (Clarke and Brown, 2007). A positive correlation was also found between serum triglycerides and PCa with an odds ratio of 1.148 (95% confidence interval 1.003-1.315; p<0.05) after correcting for age, BMI, diabetes and co medication with statin (Wuermli et al., 2005). *In vitro* studies suggested a definite relationship of lipids with prostate cell metabolism, which is also strengthened by correlation studies on human BPH or PCa 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 relationship between BPH and lipid profile and the level of correlation between lipid profile and PCa.

In conclusion, our study suggests that obesity and disturbed glucose metabolism are related to increased tumor grade and higher prostate volume in patients of prostate cancer in north 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. Differences in serum PSA, testosterone levels and prostate volume are well known parameters that may differ between healthy individuals, BPH patients, and prostate cancer patients. Our study has particularly put forth significant differences in metabolic indices and lipid profile between prostate cancer and BPH and between high and low grade prostate cancer. Among biochemical parameters, serum triglycerides and VLDL are significantly elevated in patients of prostate cancer in comparison to BPH. We accept that the sample size in our study had a limitation; therefore, further studies are needed to confirm these results. This would further help in understanding of the etiopathogenesis of BPH and prostate cancer and also in initiating targeted treatment strategies. A very few studies have been undertaken on Indian population showing association of lipids with BPH and there is always a possibility that the data in Indian population would be different from western counterparts due to racial and genetic differences.

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