ORIGINAL RESEARCH

Role of dyslipidemia, insulin and insulin-like Growth Factor-1 levels with risk of prostate cancer

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Abstract

Background and Objectives: Advanced prostate cancer is the second most frequently diagnosed malignancy and fifth leading cause of mortality in men worldwide. In India, the incidence is rapidly increasing as per the Indian Council of Medical Research report. This study aimed to estimate the serum levels of lipids, insulin, Insulin-like Growth Factor-1, prostate-specific antigen and testosterone and to identify their association with the risk of prostate cancer.

Materials and Methods: This case-control study includes 100 individuals. Cases were 50 histologically confirmed prostate adenocarcinoma patients. 50 age -matched disease free controls were included. Mean ± standard deviation in all groups were compared using the unpaired Student's t-test. Correlation analysis was used to determine the association between variables of interest and PSA, BMI among prostate cancer patients.

Results: Prostate cancer cases have significant higher level of total cholesterol, LDL, PSA, insulin and insulin-like growth factor than controls, whereas HDL and testosterone was significantly higher in controls than prostate cancer cases. Insulin levels in patients (17.54±8.44) was significantly higher than controls (13.53±4.56). Insulin had significant negative correlation with testosterone.

Conclusion: This study confirms the association between dyslipidemia and elevated serum insulin levels with increased prostate cancer risk.

Keywords: Dyslipidemia, Lipid profile, prostate cancer, insulin, insulin-like growth factor

Introduction

Prostate cancer is the most frequently diagnosed cancer in 112 countries followed by lung cancer in 36 countries and is the fifth leading cause of mortality from cancer in men globally with approximately 1.4 (7.3%) million new cases and 375,000 (3.8%) reported deaths in 2020. Incidence rates are three fold higher in high Human Development Index (HDI) countries (37.5 per 100,000) than in low HDI countries (11.3 per 100,000). Despite being a common disease, quite little evidence are available regarding its etiology. Established risk factors includes old age, race/ethnicity, family history of BPH or prostate cancer, genetic mutations, lifestyle and environmental factors [1]. In India also the incidence rates of prostate cancer are rising at a rapid pace and constitutes about 3% of the overall reported cancer cases in the country. According to ICMR National Cancer Registry Programme 2022, 43691 prostate cancer cases were reported in 2022 in India with cumulative risk of 1 in 125 and is expected to rise over 47000 cases by 2025 [2].

Androgen signaling is vital for prostate cell growth and proliferation. However, other factors like, insulin,

Insulin-like Growth factors (IGFs), lipids etc. plays an important role in the prostate cell growth and carcinogenesis [3].Alterations in the environmental and lifestyle factors such as westernization and consumption of saturated fat rich diet which leads to altered hormonal status and obesity, contributes majorly to the occurrence and progression of prostate cancer. Recent studies reported association of obesity and lipid abnormalities with increased risk of prostate cancer development, however, the available literature is inconsistent and contradictory [4].Serum testosterone, circulating insulin and IGF-1 were reported to be associated with prostate cancer in recent studies [5].

Therefore purpose of this study was to determine the differences in biochemical parameters among prostate cancer and healthy subjects and to examine the correlation among these parameters in prostate cancer cases.

Materials and Methods

Study population

This case-control study was conducted on a total of 100 individuals. From 2019 to 2021, clinical data was obtained from 50 prostate cancer patients who underwent TURP at Department of Urology, KGMU. 12 cores Trans-Rectal Ultrasound guided (TRUS) biopsy was performed on patients having serum PSA levels greater than 4ng/mL before TURP to rule out prostate cancer. Body mass index (BMI) was calculated as weight (kg)/height^2 (m^2). Patients on medication for Diabetes Mellitus, CAD, hepatic/renal diseases or testosterone replacement were excluded. Controls were 50 age-matched disease-free males, without any complications.

Specimen collection and laboratory assays

On the morning of the operation day about 2 ml blood sample was withdrawn from the antecubital vein following overnight fasting and collected in plain vial. Serum was separated from the clotted blood by centrifugation for 15 min at 3000 rpm at room temperature. Total cholesterol, HDL-C, and triglycerides (TGs) were also measured enzymatically on semi-autoanalyzer. Very low-density lipoprotein-cholesterol (VLDL-C) and LDL-C were calculated by Friedwald's formula. All hormonal assays (insulin, IGF-1 and testosterone) were measured using Enzyme-linked Immunosorbent Assay (ELISA). Insulin assay was based on sandwich principle that uses anti-insulin antibodies. Testosterone and IGF-1 assays were based on competitive binding principle that uses anti-testosterone and anti-IGF-1 antibodies respectively. All assays were performed according to manufacturer's recommendations.

Statistical analysis

This was a case-control study. Mean ± standard deviation between two and all groups were compared using the unpaired Student's t-test for continuous variables. Correlation analysis was performed to determine the association among various clinical and biochemical parameters. Statistical analyses were performed using 'GraphPad QuickCals t-test calculator'. *P* value of < 0.05 was considered statistically significant.

Ethics statement

Study was approved by the Institutional Ethics Committee, KGMU and Era University. A written informed consent was obtained from each subject.

Results

The mean age of control and prostate cancer were 59.6±7.05 and 70.24±8.44 yeas respectively. The mean BMI were 21.29±3.56 and 22.07±3.15 kg/m^2 respectively. The mean serum PSA levels were 2.78±0.96 ng/mL and 40.75±34.90 ng/mL in controls and cases respectively. The mean serum insulin levels were 13.53±4.56 ng/mL and 17.54±8.44 µIU/ml in controls and cases respectively. Total cholesterol and LDL were significantly elevated in prostate cancer patients compared to controls. However TG and VLDL shows non-significant difference in the case and control group. HDL and testosterone was significantly deceased in the diabetic group compared to controls. Additional baseline characteristics and biochemical parameters of the cases and control included in this study are presented in (Table 1).

Table 1: Baseline characteristics and biochemical parameters of PCa patients and control groups

Parameters	Control (n=50)	Cases PCa (n=50)	P value (*Significant)
Age (years), mean ± SD	55.02±9.17	70.24±8.44	< 0.0001*
n(%) <55	14 (28%)	2 (4%)	
55-64	21 (42%)	10 (20%)	
65-74	15 (30%)	22 (44%)	
≥75	0	16 (16%)	
BMI (kg/m^2), mean ± SD	20.96±3.13	22.25±3.04	0.0392*
n(%) <25	44 (88%)	40 (80%)	
≥25	6 (12%)	10 (20%)	
Total cholesterol(mg/dl)	171.75±38.11	188.19±39.30	0.0362*
Triglycerides (mg/dl)	152.20±65.25	169.86±60.27	0.1629
HDL (mg/dl)	53.33±11.41	48.60±8.79	0.0223*

LDL (mg/dl)	87.98±36.61	105.63±39.86	0.0232*
VLDL (mg/dl)	30.44±13.05	33.97±12.05	0.1631
Total PSA (ng/ml)	2.78±0.96	40.75±34.90	< 0.0001*
Insulin (µIU/ml)	13.53±4.56	17.54±8.44	0.0039*
IGF-1 (ng/ml)	335.30±35.22	360.47±27.03	0.0001*
Total Testosterone (ng/ml)	3.99±1.22	3.11±1.22	0.0005*

Pearson's correlation analysis of various biochemical parameters among prostate cancer cases was performed. Insulin showed significant negative correlation with testosterone (Figure 1) and non-significant negative correlation with PSA. (Table 2).

Table 2: Pearson's correlation of biochemical parameters among prostate cancer patients

	AGE	BMI	T. CHO	TG	HDL	LDL	VLDL	PSA	INSULIN	IGF-1	TESTO
AGE	1.000										
BMI	-0.140	1.000									
T. CHO	-0.178	0.681	1.000								
TG	-0.012	0.571	0.621	1.000							
HDL	0.090	-0.631	-0.799	-0.671	1.000						
LDL	-0.192	0.638	0.974	0.458	-0.806	1.000					
VLDL	-0.012	0.571	0.621	1.000	-0.671	0.458	1.000				
PSA	-0.030	-0.231	0.040	-0.030	-0.069	0.064	-0.030	1.000			
INSULIN	0.029	-0.036	-0.062	-0.123	-0.072	-0.008	-0.123	0.183	1.000		
IGF-1	-0.079	0.320	0.085	0.140	-0.155	0.076	0.140	0.160	0.305	1.000	
TESTO	-0.085	0.105	0.170	0.201	-0.016	0.110	0.201	0.057	-0.812	-0.133	1.000

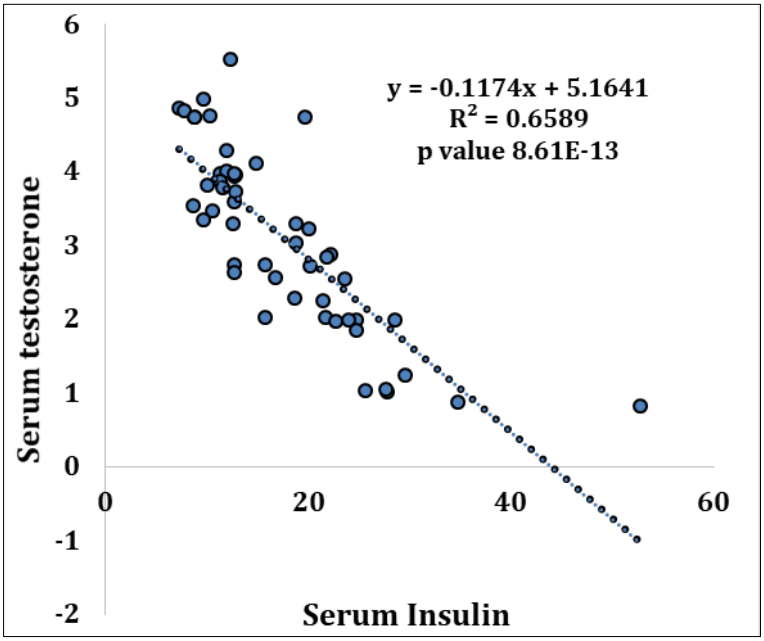

Fig 1: Scatter plot showing correlation between serum insulin and testosterone in prostate cancer patients

Discussion

Prostate cancer is major public health burden globally. Identifying and controlling the risk factors such as obesity, dyslipidemia and hyperinsulinemia before the occurrence of prostate cancer are vital to control this malignancy. The aim of our study was to find an association between dyslipidemia, insulin and IGF-1 levels with risk of prostate cancer. Ethical clearance was granted by IEC, Era University and KGMU and patients were recruited from Urology OPD after taking the written consent. Our study includes 50 Prostate cancer patients and 50 age/sex matched healthy control subjects.

In the present study, we estimated lipid profile and serum levels of insulin, insulin-like growth factor-1 and testosterone.

Large number of studies suggests a role of lipid metabolism in prostate cancer development and reported a positive association between obesity and the risk of prostate cancer which indicates that lifestyle-related risk factor influence prostate cancer progression. Kachhawa P*et al.* reported significant association of disturbed lipid profile with prostate

cancer. Allott EH *et al.* also reported association of elevated serum TG with increased risk of prostate cancer. These reporting suggests vital role of cholesterol in prostate cancer development and progression being a precursor of androgens and signaling molecule in prostate growth and differentiation [6, 7]. In the present study, we compared the mean levels of total cholesterol, TG, LDL, VLDL and HDL in prostate cases and healthy controls and observed a significant elevation of Total cholesterol and LDL in prostate cancer cases. Serum HDL levels was significantly reduced in prostate cancer cases. TG and VLDL were non-significantly elevated in prostate cancer cases. Arthur R *et al*. reported positive association of hypertriglyceridemia with high grade prostate cancer [8].Magura *et al.* conducted a hospital-based case-control study and demonstrated a significant association between hypercholesterolemia and low HDL levels with prostate cancer [9].

Insulin and IGF-1 has been reported to play a role in etiology of prostate cancer. The mitogenic and other effects of insulin and insulin-like growth factors are thought to play a role in the development of prostate cancer but the relationship between circulating insulin levels and prostate cancer risk has been unclear [10].Hyperinsulinemiaalso stimulates IGF-1 production in the liver and thus promotes prostate cancer [11]. Previous studies have associated elevated IGF-1 levels with higher risk of prostate cancer. Kim M *et al.* reported higher serum IGF-1 levels was associated with high risk of localized prostate cancer. However, serum IGF-1 levels tends to be lower in patients with higher surgical gleason score [12]. A meta-analysis of observational studies assessing serum insulin level and insulin resistance status in prostate cancer patients reported higher fasting serum insulin levels in prostate cancer patients compared to controls. Sub-group analysis showed that the elevation in serum insulin level takes place especially in patients with ages more than 65 years [13]. Another study by Di Sebastiano KM *et al.* reported a positive association of hyperinsulinemia with prostate cancer development, progression and aggressiveness [14]. Our study also reported significantly higher serum insulin and IGF-1 levels in prostate cancer cases. However, the role of insulin resistance in the development of prostate cancer needs to be confirmed in more prospective studies.

Testosterone is the major mediator of prostate cell growth which declines with age, however studies suggested that testosterone exerts differentiating effect on prostate cancer and lower level of serum testosterone might be associated with more advanced prostate cancer. Insulin resistance may lead to decreased testosterone levels due to negative feedback effect of inhibitory proteins in prostate cancer. Previous studies have also reported the association between insulin and testosterone in prostate cancer. Prabhat P *et al.* reported dyslipidemia and hyperinsulinemia to be associated with high-grade prostate cancer [15]. Our results also followed the trend of decreased levels of testosterone in prostate cancer cases. Our analysis also provides evidence for a significant negative association between serum insulin and testosterone in prostate cancer group.

Our study have several limitations like relatively smaller sample size, bias from dietary habits and exercise. Also the pathophysiological basis of hyperinsulinemia may vary among different ethnicity.

Conclusion

Prostate cancer patients had deranged lipid profile and elevated insulin levels as compared to controls. Serum insulin level was significantly negatively correlated with serum testosterone levels in prostate cancer patients which suggests insulin to be associated with the risk of prostate cancer.

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Competing interests

The authors declare no conflict of interests.

References

1. Sung H. *et al.* Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries**.** CA CANCER J CLIN 2021;71:209-249
2. Sathishkumar K, Chaturvedi M, Das P, Stephen S, Mathur P. Cancer incidence estimates for 2022 & projection for 2025: Result from National Cancer Registry Programme, India Indian Journal of Medical Research. 2022;156 (4&5):598-607. *DOI:* 10.4103/ijmr.ijmr_1821_22.
3. Lutz SZ, Hennenlotter J, Scharpf MO, Sailer C, Fritsche L, Schmid V *et al*. Androgen receptor overexpression in prostatecancer in type 2 diabetes. Molecular Metabolism. 2018; 8: 158-166.
4. Tewari R, Bajpai A, Goel A, Dalela D, Vij C. Association of metabolic parameters, lipud and cytokine profiling, androgens and insulin levels in pre cancer and prostate cancer: A cross-sectional study in North Indian set up. Journal of Medical Science and Clinical Research. 2020; 8 (5): 312-318. DOI: 10.18535/jmscr/v8i5.58.
5. Kasper JS, Liu Y, Pollak MN. Hormonal profile of diabetic men and the potential link to prostate cancer. Cancer Causes Control. 2008; 9 (7): 703-10. DOI: 10.1007/s10552-008-9133-x.

6. Kachhawa P, Kachhawa K, Agrawal D, Sinha V, Sarkar PD, Kumar S. A study of prostate cancer and its association with dyslipidemia, elevated insulin levels in blood, and relative insulin resistance prevalent in South East Asia. J Integr Nephrol Androl 2018;5:24-31.
7. Allott EH, Howard LE, Cooperberg MR, Kane CJ, Aronson WJ, Terris MK. Serum Lipid Profile and Risk of Prostate Cancer Recurrence: Results from the SEARCH Database. Epidemiol Biomarkers Prev; 23(11); 2349-56
8. Arthur R, Moller H, Garmo H, Holmberg L, Stattin P, Malmstorm H *et al*. Association between baseline serum glucose, triglycerides and total cholesterol, and prostate cancer risk categories. Cancer Medicine. 2016; 5(6): 1307-1318.
9. Magura L, Blanchard R, Hope B, Beal JR, Schwartz GG, Sahmoun AE. Hypercholesterolemia and prostate cancer: a hospital-based case-control study Cancer Causes Control 2008; 9: 259-1266.
10. Albanes D, Weinstein SJ, Tan C, Taylor PR and Virtamo J. Fasting serum insulin concentration and risk of prostate cancer. Cancer Research. 2004; 64(7): 862
11. Barnard RJ. Prostate cancer prevention by nutritional means to alleviate metabolic syndrome 23. The American Journal of Clinical Nutrition. 2007; 86(3): 889S-893S,
12. Kim M, Kim JW, Kim JK, Lee SM, Song C, Jeong IG *et al.* Association between serum levels of insulin-like growth factor-1, bioavailable testosterone, and pathologic gleason score. Cancer Medicine. 2018;1-11.
13. Elancheran R, Maruthanila VL, Mahesh Kumar, Jibon Kotoky, Kabilan S. Strategy towards Diagnosis and Treatment for Prostate Cancer. Urol Res Ther J. 2017; 1(1):115
14. Di Sebastiano KM, Pinthus JH, Duivenvoorden WCM, Mourtzakis M. Glucose impairments and insulin resistance in prostate cancer: the role of obesity, nutrition and exercise. Obes Rev. 2018 Jul;19(7):1008-1016. doi: 10.1111/obr.12674.
15. Prabhat P, Tewari R, Natu SM, Dalela D, Goel A, Tandon P *et al.* Is central obesity, hyperinsulinemia and dyslipidemia associated with high-grade prostate cancer? A descriptive cross-sectional study. Indian J Urol. 2010; 26 (4): 502-6. DOI: 10.4103/0970-1591.74440.