ORIGINAL ARTICLE

Is There Any Relation Between High-Grade Prostate Cancer and Central Obesity, Hyperinsulinemia and Dyslipidemia?

Vishal Kirti Jain[1], Madan Mohan Agrawal[2], Sher Singh Yadav[3], Neeraj Agarwal[4]

ABSTRACT

Background: Prostate Cancer (PCa) is the sixth leading cause of cancer death in men, worldwide. Incidence of prostate cancer in India is on the rise. Most studies suggest that obesity has a positive correlation with a higher risk of developing high-grade PCa and dying of PCa. Central obesity and related biochemical alterations in terms of hyperinsulinemia and dyslipidemia are associated with severity of prostate cancer in terms of high Gleason score. **Materials & Methods:** Central obesity was assessed using anthropometric measurements including waist hip ratio (WHR) and body mass index (BMI). Serum PSA, testosterone, and insulin levels were estimated. Serum levels of triglycerides (TG), cholesterol, low-density lipoprotein (LDL), and very low-density lipoprotein (VLDL), high-density lipoprotein (HDL) were also measured. Standard staging procedures were followed and for histopathological evaluation of PCa, Gleason grading was done on core biopsy tissue. **Results:** In the present population-based study, persons with high Gleason score had significantly higher WHR supporting that central obesity may predispose to high-grade prostate cancer. Study has shown a significant relationship between high Gleason score and cholesterol, TG, VLDL, and low HDL levels; however no significant relation was found with LDL levels. Testosterone is a key prostate growth factor although PCa presents at an age when testosterone levels are declining. **Conclusion:** In this study, there was no significant difference in testosterone levels in patients with high and low Gleason scores.

KEY WORDS: Prostate, Cancer, High grade, Low grade.

Introduction

Prostate cancer (PCa) is a significant global health concern, being the most commonly diagnosed cancer and ranking as the sixth leading cause of cancer-related deaths in men worldwide[1]. In recent years, the incidence of prostate cancer in India has been increasing[2]. While age, race, and family history are well-established non-modifiable risk factors for prostate cancer progression[1,3], other factors such as central obesity, hyperinsulinemia, dyslipidemia, and lifestyle changes have also been implicated[4].

The Gleason grading system is widely used to assess prostate cancer, with higher grades (8-10) being associated with a poorer prognosis compared to lower or intermediate grades (6-7)[5]. However, the relationship between obesity and prostate cancer in Western studies has yielded conflicting results, with most suggesting a positive correlation between obesity and a higher risk of developing high-grade prostate cancer and experiencing adverse outcomes[6,7]. In obese men, abdominal adiposity may also be linked to the progression of existing disease and the likelihood of biochemical recurrence following treatment[8].

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[1]Assistant Professor, Department of Urology, MGM Medical College, Indore, Madhya Pradesh, India, [2]Department of Urology , [3]Professor, Department of Urology, SMS Medical College, Jaipur, Rajasthan, India, [4]Professor, Department of Urology, SMS Medical College, Jaipur, Rajasthan, India

Address for correspondence:
Vishal Kirti Jain, Assistant Professor, Department of Urology, MGM Medical College, Indore, Madhya Pradesh, India. E-mail: kirtivishal85@gmail.com

Given potential variations in genetic and environmental factors among Indian males, this study aimed to investigate whether central obesity, along with related biochemical alterations such as hyperinsulinemia and dyslipidemia, are associated with the aggressiveness of prostate cancer, as indicated by a high Gleason score.

Material and methods

This study was designed as a cross-sectional analytical study to assess the relationship between central obesity, hyperinsulinemia, dyslipidemia, and prostate cancer aggressiveness, as indicated by Gleason scores, in a cohort of Indian males. A total of 98 male participants diagnosed with prostate cancer were recruited for this study. Participants were selected from patient came to tertiary care centre between August 2015 to December 2016. Detailed clinical information, including age, race, family history of prostate cancer, and lifestyle factors, was collected.

Central obesity was assessed by measuring waist circumference using a standardized protocol. Body mass index (BMI) was also calculated for each participant. Serum PSA, testosterone, and insulin levels were assessed. Additionally, serum levels of triglycerides (TG), cholesterol, low-density lipoprotein (LDL), very low-density lipoprotein (VLDL), and high-density lipoprotein (HDL) were analyzed. Histopathological examination of prostate tissue samples obtained during biopsies or surgeries was conducted to determine Gleason scores, which indicate prostate cancer aggressiveness.

Patients diagnosed with stage III and IV prostate cancer were included in this study (based on MRI Pelvis and bone scan) . Patients suffering from stage I and II PCa, diabetes, chronic liver, kidney, heart disease or those taking lipid lowering drugs, 5-alpha reductase inhibitors, phosphodiesterase inhibitor were excluded from the study.

On the basis of Gleason score the patients were divided in two groups— Gleason score ≥ 8 (group1); Gleason score <8 (group 2). Statistical analysis was performed using Primer Software. The relationship between central obesity, hyperinsulinemia, dyslipidemia, and Gleason scores was assessed using Student t test. The significance level was set at P value <0.05. This study was conducted following the ethical guidelines and regulations set forth by institutional ethics committee. Informed consent was obtained from all participants before their inclusion in the study. Data were analyzed using Student t test. Descriptive statistics were used to summarize participant characteristics, including means, standard deviations, and frequencies. The association between central obesity, hyperinsulinemia, dyslipidemia, and Gleason scores was examined through Student t test, with p-values indicating statistical significance.

It's important to acknowledge potential limitations of this study, such as its cross-sectional design, which limits the establishment of causality. Additionally, the sample size and the specific population studied may impact the generalizability of the findings.

Result

Out of a total of 98 patients with stage III and IV PCa, 30 had a Gleason score ≥ 8 (Group 1), while 68 patients had a Gleason score < 8 (Group 2). The mean age of the 98 patients was 63.16 years (ranging from 50 to 80), and the mean PSA was 99.8 ng/mL (ranging from 25 to 600 ng/mL). Baseline parameters, including age, PSA, and stage, are presented in Table 1. PSA levels were significantly higher in Group 2 for Stage III patients and lower in Group 2 for Stage IV patients. Group 1 patients had statistically higher mean WHR, TG levels, VLDL, cholesterol, and insulin levels, as well as lower HDL levels compared to patients in Group 2. However, serum levels of LDL and testosterone did not exhibit statistically significant differences between the two groups. Notably, Group 1 patients showed significantly higher insulin levels [Table 2]

Table 1: Baseline characteristics of study populations

Stage	Parameter	Group 1; (GS ≥ 8) N=30	Group 2; (GS <8) N=68	P value*
Stage III	Age	63.8 ± 6.9	65.2 ± 7.9	0.431
	PSA	43.26 ± 11.1	54.94 ± 9.8	<0.001
Stage IV	Age	61.19 ± 6.3	60.24 ± 9.3	0.606
	PSA	132.4 ± 87.6	97.4 ± 71.5	0.038

* P value was calculated using student t test

Discussion

While there is some evidence to suggest that obesity is associated with an increased risk of prostate cancer, the relationship is complex and not fully understood[8–10]. The present population-based study found a significant association between a high Gleason score and a higher WHR. This suggests that

Table 2: Comparison of various parameters in study groups

Parameter	Group 1; (GS ≥8) N=30	Group 2; (GS <8) N=68	P value*
WHR	0.95 ± 0.03	0.89 ± 0.02	<0.001
BMI (Kg/m^2)	27.25 ± 2.77	22.34 ± 2.63	<0.001
TG (mg/dl)	204.36 ± 76.92	164 .3± 66.12	0.009
HDL (mg/dl)	33.46 ± 6.96	37.24 ±7.23	0.016
Cholesterol (mg/dl)	180.29 ± 46.12	150.34 ± 42.31	0.003
VLDL (mg/dl)	41.32 ± 15.23	31.31 ± 13.36	0.001
LDL (mg/dl)	72.16 ± 28.35	64.31 ± 24.25	0.159
Insulin (μIU/ml)	19.12 ± 6.74	15.34 ± 6.11	0.007
Total testosterone (ng/ml)	5.14 ± 2.23	5.35 ± 2.65	0.702

* P value was calculated using student t test

central obesity, indicated by WHR, may be linked to an increased risk of high-grade prostate cancer. A higher Gleason score generally indicates a more aggressive form of prostate cancer.

Swedish Study: A study in Sweden also found an association between WHR and an increased risk of prostate cancer. This supports the idea that central obesity, as measured by WHR, may be a risk factor for prostate cancer[10]

Chinese Case-Control Study: Another case-control study conducted in China by Hsing et al. found that higher WHR was related to an increased risk of prostate cancer, particularly in men with a WHR above a certain threshold (WHR > 0.92)[11].

Rohrmann et al. found that in their study, which focused on men aged less than 55 years, the risk of high-grade prostate cancer increased with increasing BMI[12]. While these studies suggest a potential association between central obesity and prostate cancer risk, it's important to note that the evidence in this area is not entirely consistent across all studies. Some prospective studies have found less conclusive or inconsistent results regarding the relationship between central adiposity (such as waist circumference or WHR) and prostate cancer risk.

"Central obesity is linked to insulin resistance, elevated insulin levels (hyperinsulinemia), and abnormal lipid profiles (dyslipidemia). A recent study revealed that patients with high Gleason scores had notably increased insulin levels (P = 0.007). Notably, insulin is recognized for its role as a direct stimulant for in vitro prostate cell growth and is vital for the proliferation of prostate cancer cells in laboratory conditions[13]. Additionally, a study by Lehrer et al. demonstrated higher insulin levels (P = 0.033) in individuals with high-risk prostate cancer, defined by a Gleason score exceeding 7[14]. Furthermore, a case-control study in China established a statistically significant positive correlation between fasting insulin levels and the risk of developing prostate cancer"[15].

Indeed, prostate cancer cells have been observed to migrate to adipocytes within the red bone marrow, a location where metastases frequently occur. Additionally, these cancer cells are known to directly utilize lipids as an energy source for various critical processes, including tumor maintenance, proliferation, and migration. Consequently, both of these phenomena not only contribute to the progression of the disease to a more advanced stage but also enhance the survival and persistence of malignant cells[16].

"Hammarsten et al.[17] reported that among prostate cancer (PCa) patients, those with higher-grade tumors exhibited a greater degree of dyslipidemia. This was evident in their higher levels of triglycerides (TG) (P = 0.019), lower levels of high-density lipoprotein cholesterol (HDL-cholesterol) (P = 0.005), and elevated plasma insulin levels (P = 0.019) compared to individuals with lower-grade tumors. These findings align with those of Jeannette Salgado-Montilla[3]. However, a separate study conducted in the American population did not find any significant association between elevated TG and low HDL levels when comparing different grades of PCa[18]."

"Platz et al. found that men with low cholesterol levels (<200 mg/dL) had a reduced risk of developing high-grade prostate cancer (Gleason 8 to 10) compared to men with high cholesterol levels (≥200 mg/dL)[19]. The present study similarly revealed a significant association between elevated Gleason

scores and levels of cholesterol, triglycerides (TG), very-low-density lipoprotein (VLDL), and reduced levels of high-density lipoprotein (HDL). However, there was no observed relationship with low-density lipoprotein (LDL) levels." "While testosterone is recognized as a pivotal factor in prostate growth, it's noteworthy that prostate cancer (PCa) typically manifests at an age when testosterone levels naturally decline. In the context of this study, there were no notable disparities in testosterone levels between patients with high and low Gleason scores[19]. It's worth mentioning that only a limited number of studies have delved into the connection between central obesity, hyperinsulinemia, dyslipidemia, and higher-grade prostate cancer. The majority of these investigations are documented in Western literature. However, it's essential to acknowledge that our study faced limitations, notably a small sample size."

Conclusion

This research highlights the correlation between central obesity (evident in high WHR), dyslipidemia (including elevated cholesterol, LDL, TG, and low HDL levels), and hyperinsulinemia with higher-grade prostate cancer (PCa). Integrating the assessment of these lipid levels into standard screening and diagnostic protocols may offer valuable insights for patient classification and treatment planning. However, to substantiate a causative relationship between these factors and prostate cancer, as well as its severity, further investigations employing a larger sample size and prospective study design are imperative.

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