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Metabolic Syndrome & Carcinoma Prostate: Association Of Abdominal Obesity, Insulin Resistance, Hyperlipidemia And Diabetes Mellitus In Carcinoma Prostate

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ABSTRACT

Objectives : To study the effect of central obesity (waist hip ratio WHR ≥ 0.9) and biochemical parameters associated with central obesity (hyperinsulinemia, dyslipidemia, diabetes mellitus) on Gleason grading in patients of prostate cancer presenting at advanced stages

Materials and Methods : A comparative study was conducted among 68 patients having clinical stages III and IV prostate cancer at Government Medical College, Kozhikode between Aug 2011 and Aug 2012. Gleason grading on core biopsy samples was done and patients were divided in two groups-group1, Gleason score $\geq$7; group 2, Gleason score <7. WHR along with serum levels of prostate-specific antigen (PSA), testosterone, insulin, and lipid profile were done in each patient. Fasting and post prandial blood sugar levels were done in diabetic patients

Results : Two groups are similar in Age (66.34 years); range (53-80 years). Group 1 men had statistically higher mean WHR (1.06 vs 0.90), higher mean cholesterol (205 vs 180 mg/dL), higher mean low-density lipoprotein (LDL) (160 vs 110 mg/dL), than men in group 2. Serum levels of VLDL, HDL, Insulin and testosterone did not show statistically significant differences between two groups. No association could be linked between diabetes mellitus and its duration in patients with advanced stage prostate cancer.

Conclusions : This pilot study involving small number of patients Our study indicates that central obesity and dyslipidemia could be associated with high-grade prostate cancer.

Key words: Central obesity–Hyperinsulinemia–Dyslipidemia–Diabetes mellitus–Carcinoma Prostate

1 INTRODUCTION

The metabolic syndrome (MetS) also called syndrome X is a cluster condition which consist of interconnected factors which increase the risk for cardiovascular events and diabetes mellitus in a patient. The factors taken into consideration are central obesity, high serum glucose levels, dyslipidaemia, and systemic arterial hypertension.[1] Metabolic syndrome is considered a increasing public-health issue [2] and is now being considered a risk factor in multiple cancer etiology.[3] Associations between MetS components and prostate cancer (PCa) development have not been studied comprehensively; results have been divergent.[4,5,6] Prostate cancer is the most commonly diagnosed non-skin cancer and the second leading cause of cancer deaths in US men. Despite the high morbidity associated with prostate cancer, the only established risk factors are age, race, and a family history of prostate cancer. However, large geographic variation in prostate cancer risk suggests that lifestyle factors, such as westernization, may also contribute to the etiology of this disease.

Central obesity, a major factor in MetS, has been on the increase world over and also in Indian subcontinent. A study reports a prevalence of 35.1% in urban metropolitan city of Chennai.[7] Waist hip ratio (WHR) is considered to be a standard measure of central obesity and the association of WHR to PCa was studied by Hsing et al. They concluded that high levels of WHR related to excess risk for PCa.[8] In contrast there are other studies that showed no associa-

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tion between WHR and PCa. Another component of MetS that has been a topic of research is insulin. It has also been shown that insulin plays a role in etiopathogenesis of colon, prostate, pancreatic and breast cancer, but whether it increased incidence or resulted in more aggressive disease is still questionable.[9,10] Similar is the situation with dyslipidemia.

In PCa, the widely accepted grading system is Gleason.[11] Association of high grade Pca with metabolic syndrome components have been a topic of interest lately. Also, there is limited literature regarding the association between MetS and PCa at initial diagnosis. We aim to study the association of metabolic syndrome components and advanced PCa in a subset of patients in our hospital.

2 MATERIALS AND METHODS

A cross-sectional comparative study was conducted among patients having clinical stages III and IV prostate cancer who were underwent treatment in Government Medical College, Kozhikode from August 2011 to August 2012 were taken up for the study.

Basic patient profile was recorded which included age, height, weight, abdominal circumference and hip circumference. Biochemical profile of the patient was also recorded. Fasting blood sugar, fasting serum insulin level and fasting lipid profile were of particular interest for our study.

Anthropometric assessment: BMI and WHR were assessed. 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

Clinical Staging & Grading: Clinical staging was done with standard staging procedures using pretreatment parameters (DRE, needle biopsy findings, Contrast enhanced CT Scan abdomen and pelvis and bone scan). Gleason grading on core biopsy samples by histopathology was done and patients were divided in two groups-group1, Gleason score $\geq$7; group 2, Gleason score <7.

Exclusion criteria:

Chronic liver disease ,

Chronic kidney disease ,

Coronary artery disease,

Patients on lipid-lowering drugs,

Patients on 5-alpha reductase inhibitors.

The study was observational and no intervention were done except for the addition of formalized data collection

Statistical Method

Statistical analysis was done using SPSS 16.0. Paired data was compared using Wilcoxon Signed Rank test and independent groups were compared using independent samples t test. All tests were two sided and a p value<0.05 was considered to indicate statistical significance.

3 RESULTS

Of 68 patients , 34 patients were in Group 1(Gleason score $\geq$ 7) ; and 34 patients were in Group 2 . The mean age of G1 patients was 71.55 years (range 58-88), mean age of G2 patients was 70.11 years (range 59-86) ;mean PSA (92 ng/mL) range (16-156 ng/mL). All the patients were in either stage III (n = 30) or stage IV (n = 38) disease. Statistical analysis have been detailed in Table 1 **Table 1: Statistical Analysis**

Group 1 patients had statistically higher mean WHR (1.06 vs 0.90; P $\leq$ 0.004), higher mean cholesterol level (205 vs 180 mg/dL; P = 0.002), higher mean LDL (160 vs 110 mg/dL; P = 0.0005), higher mean Triglyceride (166 vs 144 mg/dl); P = 0.0005), than patients in group 2. Serum levels of VLDL, HDL, and fasting insulin did not show statistically significant differences between the two groups. Independent Samples Test have been used for the comparison. (Table 2).

Table 2: Independent Samples Test

Of 68 patients 15 patients were diabetic, 8 in G1 ; 7 in G2.Out of 8 diabetic pts. in G1, 3 had DM of <5 yr duration, 5 had DM duration of >5yr duration. (Table 3)

None of the non-diabetic patients showed insulin resistance.

Table 3: Chi-Square Test

4 DISCUSSION

Association between the MetS components and prostate cancer have been inconsistent. Obesity, which is usually assessed by Body mass index (BMI) has been associated with increased risk of prostate cancer in few studies. [12,13] The major limiting factor being the fact that Body mass index (BMI) does not differentiate fat mass from muscle mass and hence may not fully reflect the disease-related dimensions of obesity.[14] Rather than BMI, WHR a measure of Central obesity, is said to correlate more with hormonal and metabolic alterations in obesity. But the evidence for central adiposity being a risk factor for prostate cancer is meagre. Majority of these studies considered BMI as the marker of obesity. WHR as an independent predictor of prostate cancer risk regardless of BMI was proposed by the large prospective study in Swedish population.[15] Similar results were also obtained by Hsing et al in their case control study where the risk of prostate cancer was three fold (OR , 2.71, 95% CI = 1.66-4.41, P = 0.001) in patients with higher quartile (WHR > 0.92) compared with men in lowest quartile (WHR<0.86).[16] Recently there has been a shift in focus from association of central obesity to prostate cancer to its association with the grade of disease. The results of these studies are conflicting. In our study, there was a statistical association between high Gleason score with higher WHR (P<0.004). With obesity increasing in epidemic proportions in indian subcontinent further prospective studies are needed to validate the association.

Dyslipidemia was another component of MetS that we studied. In a Swedish study higher TG level and a lower HDL-cholesterol level and higher plasma insulin level were

Table 1: Statistical Analysis

GS_cat		age	Wt	Ht	BMI	WC	HC	WHR	CHO	LDL	HDL	VL	TG	Serum_Insulin	Serum_Tes
1	G1														
	Mean	71.55882	63.500000	161.4706	24.3147	100.0588	94.6471	1.0585	207.55882	157.44118	39.00000	24.9706	165.735294	7.14971	4.66382
	Std. Deviation	7.640368	9.8357727	5.54450	3.44103	9.81014	7.48689	.06752	35.020506	22.493354	4.670994	7.42022	7.9632064	5.924844	2.225257
	Minimum	58.000	33.0000	150.00	13.50	70.00	76.00	.89	144.000	92.000	29.000	12.00	150.0000	.800	1.700
	Maximum	88.000	85.0000	171.00	31.00	110.00	105.00	1.20	265.000	200.000	50.000	47.00	182.0000	22.000	8.800
2	G2														
	Mean	70.11765	58.264706	160.5588	22.5941	87.9706	96.6176	.9926	181.82353	106.91176	39.55882	24.4706	144.000000	7.54147	4.57082
	Std. Deviation	7.193283	6.1610154	5.68992	2.19724	8.77146	8.45313	.11142	28.920445	27.345564	6.267720	10.74846	8.3883035	6.114512	2.570732
	Minimum	59.000	48.0000	152.00	19.00	72.00	78.00	.88	130.000	65.000	30.000	11.00	120.0000	.200	.038
	Maximum	86.000	72.0000	176.00	30.00	104.00	109.00	1.27	280.000	201.000	50.000	56.00	158.0000	23.000	8.650

	GS_cat	N	Mean	Std. Deviation	Std. Error Mean
WHR	1	34	1.0585	.06752	.01158
	2	34	.9926	.11142	.01911

Table 2. Independent Samples Test

mean	G1[GS≥ 7]	G2 [GS< 7]	P value
WHR	1.06	0.9	0.004
Cholesterol (mg)	205	180	0.002
LDL (mg)	160	110	0.0005
Triglycerides (mg)	166	144	0.0005
HDL (mg)	39	40	0.68
VLDL (mg)	24	23	0.82
Insulin (IU/ml)	8.4	8.5	0.79

Table 3. Chi-Square Test

	G1 (GS≥7)	G2(GS<7)	P value
Diabetes	8 (no. of pts.)	7	0.77

found in patients with higher grade of prostate cancer and the associations were statistically significant.[17] Similar results could be reproduced only in African-American men and not in white men.[18] In a large prospective cohort study that included participants from Prostate Cancer prevention study, it was concluded that men with low cholesterol <200 mg/dL) had a lower risk of Gleason 8 to 10 prostate cancer [OR, 0.41; 95% CI, 0.22-0.77] than men with high cholesterol (≥ 200 mg/dL).[19] Our study depicts a statistically significant relationship between high grade disease and TG, LDL, and Cholesterol levels; however no relation was found with VLDL and HDL levels

MetS is associated with insulin resistance and hyperinsulinemia. Insulin is said to be a potent mitogen for prostate growth invitro and is a prerequisite for growth of prostate cells in culture.[20] There has been reports showing higher insulin levels in patients with high risk prostate cancer.[21] Of 68 patients, in our study 15 patients were diabetic, 8 in G1 ; 7 in G2. Out of 8 diabetic patients in G1, 3 had DM of <5 years duration, 5 had DM duration of >5 years duration. None of the non-diabetic patient showed insulin resistance. Being a small sample size, no association could be linked between diabetes mellitus and its duration in patients with advanced stage prostate cancer.

Our study indicates that central obesity and dyslipidemia may be involved in higher grade prostate cancer and that regulation of central obesity in these men or tailored treatment approaches in this high-risk population may result in better outcomes. Future studies are needed with a larger sample size to facilitate institution of appropriate therapy and reduce morbidity and cost.

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