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Original Research Article

Long term effects of various therapies on the metabolic risk factors in prostate carcinoma patients

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Abstract: The objective is to investigate the long term effects of androgen deprivation therapy and non-androgen deprivation therapy on various metabolic risk factors in prostate carcinoma patients. It was a hospital based prospective study consisted of eighty eight subjects with diagnosed prostate carcinoma and twenty five aged matched healthy controls for the comparison of basic parameters at the initial level. The prostate carcinoma subjects were divided into two groups on the basis of metastatic prostate carcinoma and locally confined prostate carcinoma viz. androgen deprivation therapy (n=51) and non-androgen deprivation therapy (n=37). The subjects were examined for Adult Treatment Panel III criteria for metabolic syndrome. Anthropometric parameters were measured and biochemical parameters estimated at baseline and after 12 and 18 months of therapy. The anthropometric and biochemical parameters were significantly increased and insulin sensitivity was significantly decreased in androgen deprivation therapy group after the therapy of 18 months. However, in non-androgen deprivation group this change was non-significant. The results of the present study suggest that men with prostate carcinoma who receive androgen deprivation therapy develop insulin resistance and hyperglycemia as compared to those who received non androgen deprivation therapy. Hence, it may be stated that androgen deprivation therapy increases the metabolic burden. However, the level of high density lipoprotein also increases significantly in androgen deprivation therapy group which shows the difference with classical metabolic syndrome.
Keywords: Prostate carcinoma, Androgen deprivation therapy, Insulin resistance, Cardiovascular disease

INTRODUCTION:

Prostate carcinoma (PCa) is a malignant tumor that usually begins in the outer part of the prostate. The worldwide PCa burden is expected to grow to 1.7 million new cases and 499 000 new deaths by 2030 simply due to the growth and aging of the global population. In India, more cases of prostate carcinoma are being picked up and it is coming to the knowledge that we are not very far behind the rate from western countries [1].

Approximately 85 percent of newly diagnosed prostate carcinoma is localized to the prostate while remaining represents invasive or metastatic disease [2]. Local surgery and/or radiotherapy (RT) are the usual treatments for men with locally confined PCa. Men with metastatic and high risk localized disease androgen deprivation are the clinical component of therapy [androgen deprivation therapy (ADT)], either alone or in combination with other modalities. The modalities of ADT are surgical (bilateral [B/L] orchiectomy) or medical (gonadotropin-releasing hormone [GnRH] agonists or antagonists), with most patients choosing the medical option. The aim of ADT is to achieve serum testosterone levels as low as possible, with guidelines recommending levels below 50ng/dl (1.7 m mol/litre) [3]. [Normal range in young men, 300-1000 ng/dl [4]]. Despite the efficacy of androgen suppression

therapy, this therapy may lead to metabolic abnormalities which lead to the development of insulin resistance and metabolic syndrome. It is also associated with adverse effect on bone, sexual function and cognitive health as compared with men who only underwent local surgery and/or received radiation therapy. Epidemiological studies have shown that men with low levels of male sex hormones (testosterone) are more prone to develop diabetes mellitus than their eugonadal counterparts [5].

Men who are receiving androgen deprivation therapy provide an excellent model to study the adverse effects of hypogonadism as they have castrate levels of testosterone. Non androgen deprivation therapy (non-ADT) allows us to assess the effect of prostate carcinoma on these metabolic parameters. Various risk factors have been studied in prostate carcinoma but long term effects of therapies had a scope to be explored. Hence, the present study was undertaken to investigate the long term effects of various therapies (ADT and Non ADT) in prostate carcinoma patients on various metabolic risk factors.

MATERIAL AND METHODS:

The present study was conducted in the Department Of Biochemistry, Rajasthan University of Health Sciences College of Medical Sciences (RUHS-CMS), Jaipur and Bhagwan Mahaveer Cancer Hospital & Research Centre (BMCHRC), Jaipur, This was a hospital based prospective study and study duration was 1 year and six months. Eighty eight subjects with diagnosed prostate carcinoma that attended the outpatient clinics or admitted in the various wards of Bhagwan Mahaveer Carcinoma Hospital and Research Centre, Jaipur, were recruited in the study.Informed consent was obtained from the participants and the study protocol was reviewed and approved by the institutional ethics committee before initiation of the study.The age group of prostate carcinoma patients was 58-64 years. These subjects were divided into two group's viz. ADT (51) and non-ADT (37) on the basis of metastatic prostate carcinoma and locally confined prostate carcinoma, respectively. ADT group was further classified into two subgroups viz. GnRH (n=18) and B/L orchiectomy (n=33) on the basis of modalities of ADT include medical therapy (GnRH agonist or antagonist) or surgery (bilateral orchiectomy), respectively. In non- ADT group 37 age matched eugonandal subjects with non-metastatic prostate carcinoma who had undergone prostatectomy and/or received radiotherapy (RT) was further classified into subgroups viz. total prostatectomy (n=8) and RT (n=29). Each case was called for follow up at 12 months and 2nd follow up at 18 month from the enrollment in the study. Physical and clinical examination of each subject was carried out at the time of registration and then after 12 and 18 months of receiving scheduled treatment. They were also interviewed for food habits, daily calorie intake life style attributes including smoking, use of alcohol and physical activity. Before the prostate carcinoma subjects were subjected to different treatments as advised by the clinician or consultant, they were all assessed for metabolic abnormalities as per ATP III and prevalence of metabolic syndrome in the study group before and after 12 and 18 month of therapy.

According to Adult Treatment Panel (ATP) III criteria a participant must have 3 or more following criteria for establishing metabolic syndrome [6].

1. Abdominal obesity (waist circumference) > 102 cm in men and waist circumference > 88 cm in women
2. Hypertriglyceridemia ≥ 150 mg/dl or 1.69 mmol/litre
3. Low high density lipoprotein-Cholesterol (< 40 mg/dl or 1.04 mmol/liter in men and < 50 mg/dl or 1.29 mmol/litre in women
4. High blood pressure (BP) ≥ 130/85 mmHg
5. High fasting glucose level ≥ 110 mg/dl or 6.1 mmole/litre

For the comparison of basic parameters at the initial level 25 age matched health controls were also included in the present study which were selected from volunteers includes doctors, resident doctors, paramedical staff and healthy relatives/attendants of patient, normal eugonandal men (serum testosterone level 3-10 ng/dl) who had normal prostate specific antigen levels. Exclusion criteria included those who had abnormal liver function tests or renal function tests, steroids used in the previous few months, a history of thyroid disease or any form of hypogonadism, prior to the diagnosis of prostate carcinoma.

Venous blood from each subject after overnight fast was drawn from anticubital vein by using aseptic techniques in fluoride vial (1ml) for plasma glucose estimation and in plain vial (5ml) for other parameters and plasma or serum was separated. Anthropometric assessment was done by measuring blood pressure, body weight (kg) and height (m) without shoes and/or cap andbody mass index (BMI) was calculated as weight (kg)/height (meter) ^{2}. Biochemical parameters were analyzed on fully automated analyzer-Randox Imola by using commercially available kits of Randox which included fasting plasma glucose by GOD-PAP method [7], serum lipid profile [serum total cholesterol(TC) by CHOD PAP method, serum triglycerides (TG) by GPO/PAP method [8], high density lipoprotein cholesterol (HDL) and low density lipoprotein cholesterol (LDL) by direct homogenous method [9] very low density lipoprotein cholesterol (VLDL) was calculated by Friedewald's formula [10] and serum free fatty acids(FFA) by colorimetric method [11]. Fasting serum insulin was estimated by direct immunoenzymatic method [12], serum testosterone [13] and prostate specific antigen (PSA) was performed by enzyme linked sorbent assay (ELISA) [14] provided by Yark diagnostic Private Limited. Insulin resistance (IR)

was calculated by homeostasis model assessment index (HOMA) [15]. HOMA-IR= {Serum Insulin (μIU/mL) X Fasting Plasma Glucose (mg %)} / 405.and insulin sensitivity (IS) was calculated by quantitative insulin sensitivity check index (QUICKI) [16]. QUICKI - IS = 1/ log fasting glucose (mmol/L) + log fasting insulin (mmol/L).

STATISTICAL ANALYSIS

Statistical analysis was done by student's test and results were shown as mean ±standard deviation (SD). Value $P<0.05$ was accepted as statistically significant. Pearson's correlation test was used to assess the correlation.

RESULTS:

The mean age of the patients studied in the present study was 61.04. At baseline, a non-significant difference was observed in anthropometric and biochemical parameters in control and prostate carcinoma subjects except in the levels of serum insulin, serum triglycerides, VLDL and PSA as shown in Table1.

After the therapy of 12 months the change in BMI was non-significant in ADT group but a significant change was observed in BMI after18 months of therapy in the subject's undergone treatment with ADT (i.e. 21.69± 1.26 in the GnRH subgroup and 23.19± 0.92 in the B/L orchiectomy subgroup).In non-ADT group a non-significant change was observed in BMI after the therapy of 12 and 18 months (Table 3). The biochemical parameters viz. fasting plasma glucose, insulin, insulin resistance (IR-4.18± 1.71 in GnRH subgroup and 5.61± 2.73 in B/L orchiectomy subgroup), serum lipid profile level viz. TG, TC, HDL, LDL and VLDL increased significantly after the therapy of 12 months in the subjects undergone treatment with ADT. Similar trend was observed in all biochemical parameters after the therapy of 18 months in ADT group (Table 2). Whereas, no such change was found in subjects with non- ADT treatment after the therapy of 12 and 18 months (Table 3). However, insulin sensitivity (0.456± 0.046 in the GnRH and 0.453± 0.040in the B/L orchiectomy subgroup), level of testosterone and PSA were decreased significantly in GnRH and B/L orchiectomy subgroups (ADT group) after 12 and 18 months of therapy (Table2). Level of PSA (25.32± 25.32 in the RT subgroup and 16.58± 8.15 in the total prostatectomy subgroup) was also decreased significantly in radiotherapy and total prostatectomy subgroups (non-ADT group) after 12 and 18 months of therapy but the change in insulin sensitivity and in level of testosterone in non-ADT group was non-significant (Table3).

In the GnRH subgroup, levels of serum insulin, serum FFA, and insulin resistance also increased significantly and insulin sensitivity decreased significantly between the therapy of 12 and 18 months. However, in the B/L orchiectomy subgroup levels of TC also increases along with other parameters viz. serum insulin, serum FFA and insulin resistance between 12 and 18 months of therapy (Table 2) whereas no such change was found in anthropometric and biochemical parameters of non-ADT group (Table 3).

A significant negative correlation of insulin resistance and HDL (graph 1 and 3 r^2=0.29 and r^2 =0.35 for insulin resistance and HDL, respectively) and a significant positive correlation of insulin sensitivity with testosterone level in ADT was observed in the study (graph 2, r^2=0.13). Similarly, a significant positive correlation of HDL and a negative correlation of insulin sensitivity with insulin resistance in ADT group was observed in the study (graph 4 and 5, r^2 = 0.201and r^2 = 0.686 for HDL and insulin sensitivity, respectively).

Table-1: Anthropometric and Biochemical parameters in controls and prostate carcinoma subjects before therapy

Parameters	Controls (25)	P Ca (88)	Statistical correlation
BMI (kg/m2)	20.57 ± 1.04	20.98 ± 1.36	0.035
Fasting plasma glucose (mg/dl)	90.88 ± 11.14	91.63 ± 12.00	0.777
Insulin (μU/ml)	3.33 ± 1.28	5.95 ± 2.23	0.000
Insulin Resistance	0.898 ± 0.547	1.35 ± 0.567	0.000
Insulin Sensitivity	0.647 ± 0.056	0.612 ± 0.07	0.005
Triglycerides (mg/dl)	72.92± 37.81	105.10 ± 31.17	0.000
Total cholesterol (mg/dl)	137.56± 27.74	143.17 ± 32.45	0.434
HDL (mg/dl)	47.12±6.26	45.54 ± 6.19	0.264
LDL (mg/dl)	75.85± 25.67	76.6 ± 31.07	0.935
VLDL (mg/dl)	14.58± 7.56	21.02 ± 6.23	0.000
Free fatty acids (mg/dl)	0.168± 0.045	0.174 ± 0.122	0.810
Testosterone (μU/ml)	581.92 ± 66.50	625.49 ± 164.04	0.198
PSA (ng/ml)	0.88 ± 0.33	85.93 ± 114.99	0.000

Significant change: $P = 0.000$

Table 2: Anthropometric and Biochemical parameters after 12 and 18 months of therapy in ADT (GnRH and B/L orchiectomy subgroups) group

Parameters	ADT							
	GnRH therapy (n=18)				B/L orchiectomy (n=33)			
	Before Therapy	After 12 Months	After 18 Months	ANOVA (2-tailed)	Before Therapy	After 12 Months	After 18 Months	ANOVA (2-tailed)
BMI (kg/m2)	19.94 ±1.33	20.63 ±1.52	21.69 ±1.26	.002*	21.42 ±1.55	22.65 ±1.72	23.19 ±0.91	0.000”
Fasting plasma glucose (mg/dl)	93.5 ±14.60	115.4 ±15.41	136.33 ±32.39	0.000 *	91.96 ±12.70	125.75 ±41.82	151.57 ±49.13	0.000*
Insulin (µU/ml)	5.92 ±2.90	14.27 ±4.59	22.49 ±9.26	0.000 **	6.57 ±2.02	17.54 ±5.78	23.53 ±7.99	0.000**
Insulin Resistance	1.38 ±0.737	4.18 ±1.71	8.49 ±4.70	0.000**	1.46 ±0.54	5.61 ±2.73	9.50 ±5.76	0.000**
Insulin Sensitivity	0.632 ±0.017	0..497 ±0.03	0.456 ±0.046	0.000**	0.591 ±0.053	0.478 ±0.036	0.453 ±0.040	0.000*
Triglycerides (mg/dl)	98.94 ±36.83	184.33 ±64.04	243.72 ±170.92	0.001*	114.5 ±27.82	188 ±91.35	223.03 ±87.10	0.000”
Total cholesterol (mg/dl)	139.94 ±35.85	207 ±42.42	230.11 ±57.30	0.000”	145.03 ±31.26	228.84 ±40.81	267.03 ±49.21	0.000**
HDL (mg/dl)	42.72 ±6.31	50.88 ±9.28	54.5 ±12.55	0.002*	46.21 ±7.36	51.96 ±11	56.09 ± 10.8	0.000*
LDL (mg/dl)	77.4 ±31.91	119.24 ±35.80	126.86 ±38.63	0.001”	75.90 ±30.70	139.27 ±33.90	166.33 ± 40.59	0.000”
VLDL (mg/dl)	19.78 ±7.36	36.86 ±12.80	48.74 ± 34.18	0.000*	22.90 ±5.56	37.6 ±18.27	44.60 ±17.42	0.000”
Free fatty acids (mg/dl)	0.248 ±0.186	0.281 ±0.198	0.564 ± 0.247	0.001**	0.157 ±0.06	0.350 ±0.123	0.597 ±0.256	0.000**
Testosterone (µU/ml)	689.13 ±198.64	30.98 ±11.61	29.75 ±13.76	0.000”	598.65 ±180.88	35.05 ±12.39	33.75 ± 11.98	0.000”
PSA (ng/ml)	95.06 ±146.72	31.22 ±39.20	25.56 ±45.01	0.005”	86.93 ±112.62	33.30 ±42.76	11.88 ± 19.08	0.000*

*: change between baseline & 18 months was significant while change between baseline &12 months and 12 & 18 months was non-significant by post hoc test, “: change between baseline and after 12 months & 18 months were significant, **: change between baseline, after 12 months & 18 months, between 12 & 18 months were significant by post hoc test. ***: change between baseline & after 18 months and in between 12 & 18 months was significant by post hoc test.

Table 3: Anthropometric and Biochemical parameters after 12 and 18 months of therapy in Non-ADT (radiotherapy and total prostatectomy subgroups) group

Parameters	Non ADT							
	Radiotherapy (n=29)				Total prostatectomy (n=8)			
	Before Therapy	After 12 Months	After 18 Months	ANOVA (2-tailed)	Before Therapy	After 12 Months	After 18 Months	ANOVA (2-tailed)
BMI (kg/m2)	20.99 ±0.86	21.91 ±0.87	21.91±0.87	0.897	21.48 ±0.990	21.80 ± 0.743	21.84 ± 0.642	0.488
Fasting plasma glucose (mg/dl)	89.79 ±9.55	95.34 ±11.11	99.24 ±8.22	0.006	92.75 ±12.05	93.62 ± 11.07	94 ±18.18	93.5 ±14.60
Insulin (µU/ml)	5.67 ±2.03	7.84 ±0.511	7.83 ±0.585	0.009	4.41 ±1.85	5.91 ± 1.48	6.05 ±1.65	5.92 ±2.90
Insulin Resistance	1.26 ±0.47	1.84 ±0.25	1.91 ±0.217	0.084	1.03 ±0.393	1.34 ± 0.232	1.45 ±0.61	1.38 ±0.737
Insulin Sensitivity	0.616 ±0.064	0.476 ±0.008	0.475 ±0.009	0.079	0.643 ±0.038	0.599 ± 0.03	0.598 ±0.039	0.632 ±0.017
Triglycerides (mg/dl)	96.37 ±28.36	114.27 ±21.92	115.41 ±23.17	0.006	111.62 ±33.83	102 ±37.29	104.87±32.62	98.94 ±36.83
Total cholesterol (mg/dl)	135.89 ±26.71	164.41 ±29.48	167.03 ±29.17	0.008	169.12 ±40.15	155.87 ±54.22	162.75±48.02	139.94 ±35.85
HDL (mg/dl)	46.86 ±4.24	43.96 ±4.76	43.75 ±5.37	0.027	44.37 ±5.42	40.25 ±4.89	39.12±4.70	42.72 ±6.31
LDL (mg/dl)	69.75 ±25.10	97.59 ±29.85	100.19 ±32.06	0.008	102.42 ±41.65	95.22 ±56.83	102.65 ±45.57	77.4 ±31.91
VLDL (mg/dl)	19.27 ±5.67	22.85 ±4.38	23.08 ±4.63	0.006	22.32 ±6.76	20.40 ±7.37	20.97 ±6.52	19.78 ±7.36
Free fatty acids (mg/dl)	0.134 ±0.026	0.173 ±0.061	0.192 ±0.07	0.008	0.221 ±0.234	0.217 ±0.198	0.386 ±0.317	0.248 ±0.186
Testosterone (µU/ml)	634.60 ±81.66	653.03 ±82.9	588.72 ± 80.58	0.011	560 ±208.17	583.75 ±127.69	551.37 ±136.28	689.13 ±198.64
PSA (ng/ml)	67.59 ±57.28	24.75 ±27.19	25.32 ± 25.32	0.002”	127.8 ±193.21	13.56 ±7.75	16.58 ± 8.15	0.005”

“: change between baseline and after 12 months & 18 months were significant

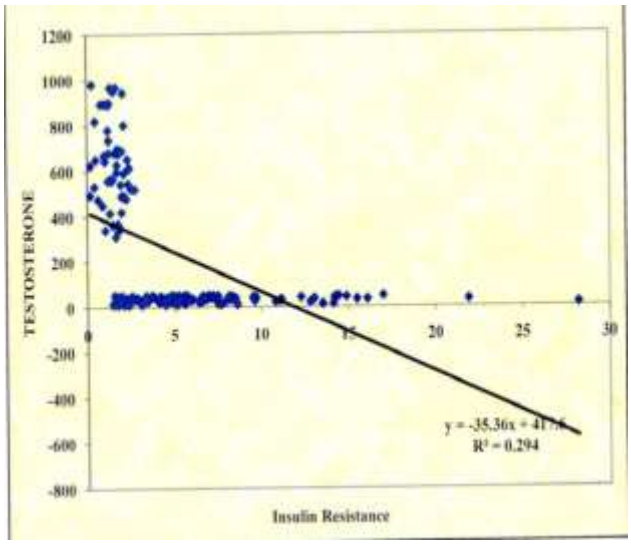

Fig 1: Testosterone in ADT Group during the Study Period

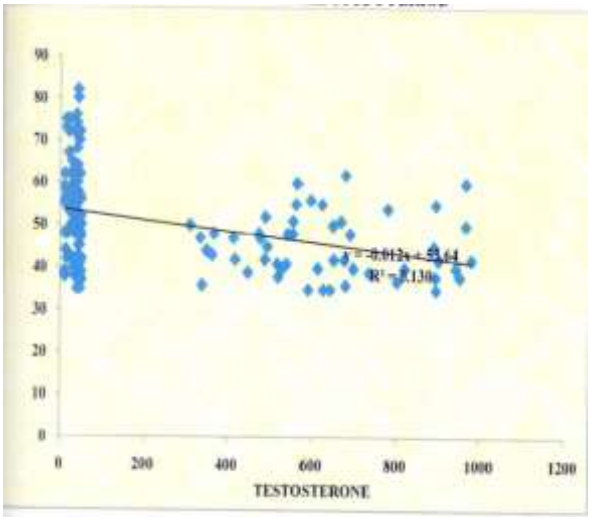

Fig 2: Correlation of HDL with Testosterone in ADT Group during the Study Period

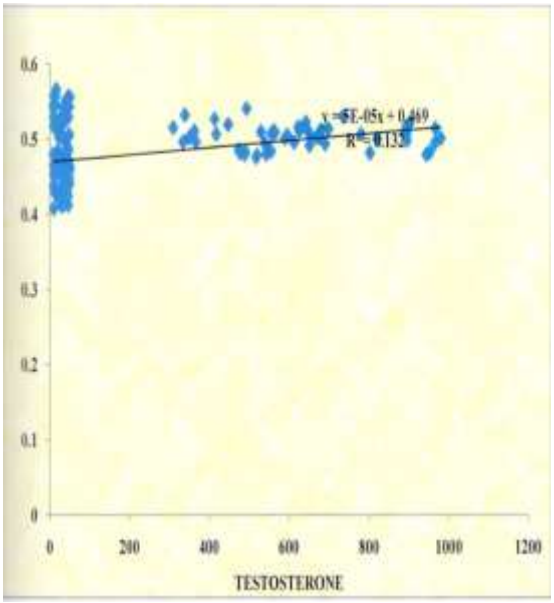

Fig 3: Correlation of Insulin Sensitivity with Testosterone in ADT Group during the Study Period

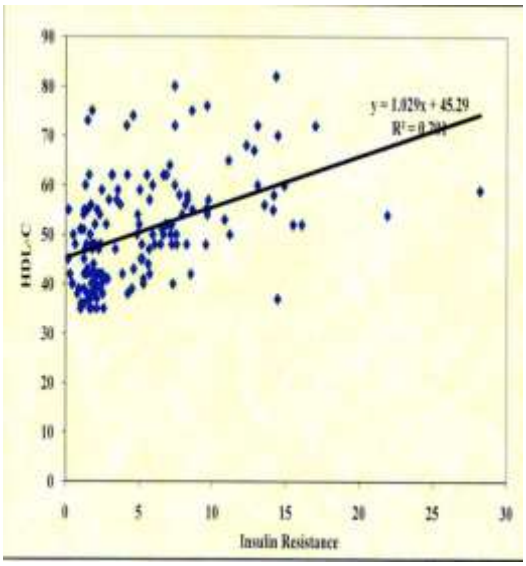

Fig 4: Correlation of HDL with Insulin Resistance in ADT Group during the Study Period

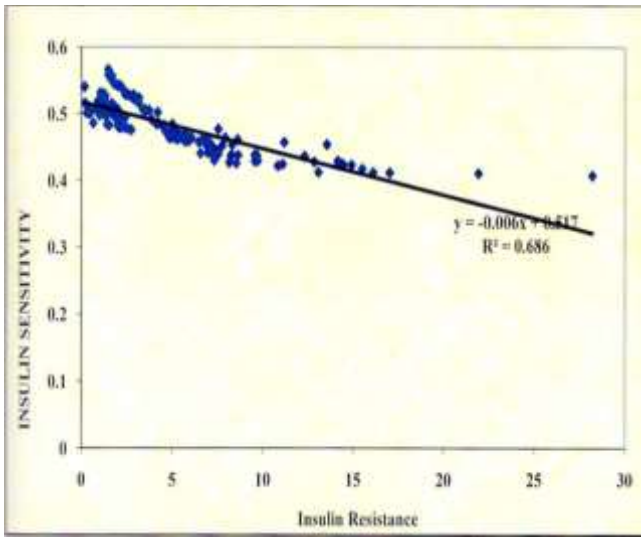

Fig 5: Insulin Resistance in ADT Group during the Study Period

DISCUSSION:

Although prostate carcinoma is a leading cause of death in men, approximately 50% of men who are diagnosed with prostate carcinoma die of other, unrelated causes. Of these, cardiovascular disease is one of the most common causes of death [17]. At baseline, anthropometric and biochemical parameters of prostate carcinoma subjects and controls except insulin showed a non-significant difference as shown in Table 1. The levels of insulin were significantly higher in prostate carcinoma patients as compared to controls. This may be due to the fact that insulin is a known growth factor and there is a possibility that insulin may be responsible for the stimulation of prostate carcinoma cells.

Further, it was observed in the present study that the level of serum lipid profile (viz.TC, TG, HDL, LDL and VLDL) in prostate carcinoma subjects and controls were comparable at baseline, except triglycerides which was significantly higher in those with prostate carcinoma. VLDL is also showed an increase over control values which are in concurrence with the clinical studies reporting the positive correlation between increase dietary fat intake and higher incidence of prostate carcinoma [18]. As shown in Table 1 the testosterone levels were found to be higher in subjects with prostate carcinoma as compared to controls. However, the difference was not found to be statistically significant at the baseline as prostate carcinoma has been recognized as an androgen sensitive disease since the seminal work of Huggins and Hodges in 1941[19]. Prostate specific antigen is a known marker for prostate carcinoma was found to be significantly higher in prostate carcinoma subjects as compare to controls.

The study population was divided into two groups according to the type of therapy given i.e. ADT and non-ADT. After the therapy of 18 months a

significant increase in BMI was observed in subject's undergone treatment with ADT (Table 2) whereas no such change was found in subjects with non-ADT treatment (Table 3). This indicates that ADT is associated with increase in fat mass and it can be attributed to the fact that androgens are important determinants of body composition and they promote lean body mass over fat mass.

It was observed in the present study that the biochemical parameters viz. fasting plasma glucose, insulin and insulin resistance and serum FFA level were significantly increased and insulin sensitivity was significantly decreased in GnRH and B/L orchiectomy (Table 2) while in RT and total prostatectomy subgroups this change was non-significant (Table 3). The results clearly indicate that ADT increases insulin resistance which is an independent risk factor for cardiovascular disease. It also gives rise to impaired insulin sensitivity which increases the risk of diabetes, cardiovascular disease, myocardial infarction and sudden death. Our observations suggest that ADT in men with prostate carcinoma leads to the development of insulin resistance and diabetes mellitus. This may be attributed to fact that low testosterone level gives rise to excessive hepatic gluconeogenesis, impaired peripheral glucose use and increased lipolysis leading to increased free fatty acids are the hallmarks of insulin resistance found in metabolic syndrome.

In the present study, all lipid profile parameters after 12 and 18 months of therapy in GnRH and B/L orchiectomy subgroups were increased significantly (Table 2) while in radiotherapy and total prostatectomy subgroups there was no significant change observed in lipid parameters (Table 3).Since, hyperlipidemia is a known metabolic risk factor for cardiovascular disease and is invariably associated with insulin resistance and hyperinsulinemia and insulin resistance is an important condition for metabolic syndrome.

The increase in HDL in the present study shows the difference with classical metabolic syndrome which may be due to the fact that testosterone may actually decrease HDL concentrations and have a potentially atherogenic effect but testosterone induced decrease in HDL is specifically in HDL3c, which is thought to be the least anti-atherogenic sub fraction. The findings of the present study indicates that the adverse metabolic profile observed in men who received ADT (Table 2) as compare to those who receives non-ADT (Table 3) may be responsible for higher risk of developing diabetes and cardiovascular disease in this population. These findings are in agreement with evidence suggesting that male hypogonadism is associated with higher cardiovascular mortality and that testosterone replacement therapy (TRT) in hypogonadal men results in reducing blood pressure (BP) and improves insulin sensitivity and lipid profiles. Testosterone may possess anti-inflammatory and anticoagulation properties and therefore TRT contributes to reduction in carotid intima media thickness [20].

Level of testosterone and PSA decreased significantly in GnRH and B/L orchiectomy subgroup (ADT group) after 12 and 18 months of therapy (Table 2). These findings are supported by the study of William P Harris *et al.;* in 2009 [2]. This is attributed to the fact that ADT reduces serum testosterone to anorchid levels within 12 hours, with rapid reduction of tumor burden in men with prostate carcinoma. However, in radiotherapy and total prostatectomy subgroups (non-ADT group) there was no significant change observed in the levels of testosterone after 12 and 18 months but the level of PSA was significantly decreased (Table 3). This is because radiation therapy is the use of high-energy in X-rays, electron beams or radioactive isotopes which kills carcinoma cells and shrinks tumors. It ionizes or damages the chromosomes in the cell so that they cannot multiply while total prostatectomy (radical prostatectomy) is the complete removal of the prostate is one of the most common treatments for prostate carcinoma which removes the prostate gland for qualifying prostate carcinoma patients.

Our study indicates that there is a significant increase in metabolic syndrome risk factors in the subject's undergone ADT treatment while in the subjects receiving non ADT treatment no significant change was observed in metabolic syndrome risk factors. Further studies need to be explored as the findings of the present study show increased HDL which is distinct from classically defined metabolic syndrome.

CONCLUSION:

In conclusion, the results of the present study suggest that men with prostate carcinoma who receive androgen deprivation therapy develop insulin resistance and hyperglycemia as compared to those who received non androgen deprivation therapy. This adverse metabolic profile is independent of age and BMI and is a direct result of hypogonadism. It may be stated that ADT adversely affects metabolic risk factors which are associated with insulin resistance, diabetes and CVD. Hence, ADT increases the metabolic burden. The findings indicate that screening of patients during therapy for metabolic risk factors may prevent complications due to metabolic syndrome.

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Competing Interests:

Authors have declared that no competing interests exist.

Compliance with ethical standards

.**Informed consent** Informed consent was obtained from all individual participants included in the study.

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