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ADVERSE EFFECT OF ANDROGEN DEPRIVATION THERAPY ON METABOLIC SYNDROME AND ITS COMPONENTS IN METASTATIC PROSTATE CARCINOMA PATIENTS

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ABSTRACT

Objective: Study was done to investigate the adverse effects of androgen-deprivation therapy on metabolic syndrome and its components in metastatic prostate carcinoma patients.

Material and Methods: It was a hospital-based prospective study comprising fifty-one subjects with diagnosed metastatic prostate carcinoma. The subjects receiving androgen deprivation therapy were classified into two groups, one group including patients who have received gonadotropin-releasing hormone (n=18) and another group including patients with bilateral orchiectomy (n=33) on the basis of the modalities of androgen deprivation therapy. Measurement of the anthropometric parameters viz. blood pressure, body weight, height, body mass index and biochemical parameters viz. fasting plasma glucose, fasting insulin, insulin resistance and insulin sensitivity, total lipids, phospholipids, total cholesterol, triglycerides**,** high density lipoprotein, low density lipoprotein and very low density lipoprotein cholesterol, free fatty acid, levels of testosterone and prostate-specific antigen were done and the subjects were examined for Adult Treatment Panel III (ATP-III) criteria for metabolic syndrome.

Results: A significant rise was observed in the waist circumference and biochemical parameters and insulin sensitivity and also the level of testosterone and prostate-specific antigen were significantly decreased after the androgen deprivation therapy (i.e. orchiectomy and medical therapy) of 18 months.

Conclusions: The results of the present study suggest that androgen deprivation therapy adversely affects the metabolic risk factors as identified by Adult Treatment Panel III and also increases the risk of diabetes and cardiovascular disease.

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Keywords: Prostate carcinoma, Androgen deprivation therapy, Metabolic syndrome, Diabetes mellitus

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Introduction

Prostate carcinoma (P Ca) is the second common cause of cancer related mortality in men in the United States [1]. As per the Indian Council of Medical Research (ICMR), it is the second most common cancer in Indian males. The incidence rate is 9-10/100,000 population which is higher than other parts of Asia and Africa but lower than the United States of America and Europe [2]. It is a disease of men above the age of 50 years and its prevalence increases with the increase of age. It was in year1941 that Huggins and colleagues described the androgen-dependence of prostate carcinoma [3] and androgen-deprivation therapy (ADT) has in recent decades become a common mode of therapy in men with recurrent or metastatic prostate carcinoma, either alone or in combination with other modalities. ADT can be accomplished either by surgical or bilateral [B/L] orchiectomy (castration) or medical orchiectomy (using either a gonadotropin-releasing hormone [GnRH] agonist or a GnRH antagonist). In some cases, anti-androgens have been combined with a GnRH agonist to block the effects of androgen produced by the adrenal gland and produce a combined androgen blockade. Both medical orchiectomy and surgical orchiectomy are appropriate methods for lowering serum testosterone levels in men with advanced castration sensitive prostate carcinoma [4]. The decision between medical and surgical treatment is based upon a variety of factors including patient's preference, cost, and treatment availability. The aim of ADT is to achieve serum testosterone levels as low as possible, with guidelines recommending levels below 50 ng/dl (1.7mmol/l) [5] (normal range in young men, 300-1000 ng/dl [6]). Despite the efficacy of androgen deprivation therapy, accumulating evidence also indicates that this therapy may lead to metabolic abnormalities which give rise to the insulin resistance and metabolic syndrome [7].It is also associated with an adverse effect on bone, sexual function and cognitive health [8].Recent research has shown that men with Prostate carcinoma (P Ca) have higher cardiovascular mortality [9].

Because insulin resistance is independently associated with cardiovascular mortality [10], it is possible that this, at least partly, may explain the higher cardiovascular mortality in this population (with hypogonadism as the

main trigger of these events). Metabolic syndrome is a known risk factor for cardiovascular mortality [10]; however, the presence of metabolic syndrome in men with Prostate carcinoma (P Ca) undergoing ADT has not been evaluated. Therefore, it is important for caregivers and patients to be aware of the adverse consequences of ADT. Hence, the present study was undertaken to evaluate the adverse effects of ADT on metabolic syndrome and its components in metastatic prostate carcinoma patients as identified by the Adult Treatment Panel III (ATP III).

Materials and Methods

The present study was conducted at the Department of Biochemistry of government medical college of Jaipur, Rajasthan and Bhagwan Mahaveer Cancer Hospital and Research Centre (BMCHRC), Jaipur. This was a hospital-based prospective study and the duration of the study was one year and six months. Fifty-one subjects with diagnosed metastatic prostate carcinoma who attended in the outpatient clinics or admitted in the various wards of the Department of Urology of medical college & its associated group of hospitals and Bhagwan Mahaveer Cancer Hospital and Research Centre, Jaipur, were recruited in the study. The age group of metastatic prostate carcinoma patients was 58-64years.These subjects were divided into two group's viz. subjects on medical therapy with GnRH (n=18) and subjects on bilateral orchiectomy (B/L) orchiectomy therapy (n=33) on the basis of modalities of ADT. Each subject was called for 1st follow-up at 12 months and 2nd follow up at 18 months from the date of 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, lifestyle attributes including smoking, use of alcohol and physical activity. General physical examination was done, and vital parameters were recorded. All the subjects were examined for various risk factors pronounced in ATP III for establishing the prevalence of metabolic syndrome in the study group before and after 12 and 18 months of therapy.

According to ATP III criteria a participant must have three or more following criteria for establishing metabolic syndrome:[11]

(1) Abdominal obesity [waist circumference (WC)]> 102 cm in men and> 88 cm in women

(2) Hypertriglyceridemia ≥ 150 mg/dl or 1.69 mmol/l

(3) Low high-density lipoprotein (HDL)-cholesterol (< 40 mg/dl or 1.04 m mol/l in men and < 50 mg/dl or 1.29 m mol/l in women)

(4) High blood pressure ≥ 130/85 mmHg

(5) High fasting glucose level ≥ 110 mg/dl or 6.1 m mol/l

For the comparison of basic parameters at the initial level, twenty five age-matched healthy controls were also included in the present study who were selected from volunteers including doctors, resident doctors, paramedical staff and healthy relatives/attendants of patient, normal eugonadal men (serum testosterone level 3-10 ng/dl) who had normal prostate-specific antigen (PSA) levels. Written informed consent of subjects was taken prior to their inclusion in the study. Exclusion criteria included those who had abnormal liver function test or renal function test, steroid use 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 an overnight fast was drawn from antecubital vein by using aseptic techniques in plain vacutainers and serum was separated. The anthropometric assessment was done by measuring body weight (Kg) and height (m) without shoes and/or cap and body mass index (BMI) was expressed as weight per height square [12]. Biochemical parameters were analyzed on fully automatic analyzer of Beckman Coulter (AU 680) which included fasting plasma glucose by GOD-POD method[13], serum total lipids (TL) by phosphovanillin method[14], serum phospholipids (PL) by Trinder's phenol method[14], serum total cholesterol [TC] by CHOD PAP method[14],serum triglycerides [TG] by GPO/PAP method[14],high density lipoprotein [HDL] and low density lipoprotein [LDL] cholesterol by direct homogenous method[15]. Serum-free fatty [FFA] acid estimation was done by the colorimetric method [16]. Very low-density lipoprotein [VLDL] cholesterol was calculated by using the Friedwald's[17]formula. Fasting serum insulin estimation was done by direct immunoenzymatic method [18] and serum testosterone [19] and PSA[20] were performed by enzyme-linked sorbent assay (ELISA). Insulin resistance was calculated by the homeostasis model assessment index (HOMA-IR) [21] and insulin sensitivity was calculated by quantitative insulin sensitivity check index (QUICKI)[22].

Statistical Analysis

Statistical analysis was done by using Microsoft excel and Student's 't' test was applied. 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 and Discussion

Metabolic syndrome is related to cardiovascular disease or type II diabetes; however, the relationship between metabolic syndrome and prostate cancer is unclear. It has been reported that incidence and mortality rates of colon cancer, endometrial cancer and breast cancer are associated with components of metabolic syndrome such as obesity and insulin resistance [23]. Epidemiologic evidence suggests that low testosterone levels in men predict the development of metabolic syndrome [24]. Because men with metastatic P Ca undergoing ADT have castrated levels of testosterone, they provide an excellent model to study the association between hypogonadism and metabolic syndrome. Thus, in view of this, the present study was conducted on fifty-one male metastatic prostate carcinoma patients with mean age 60.66± 4.20 years and twenty -five age-matched healthy control subjects were included in the study for the comparison of basic parameters at the initial level with mean age 61.04 ± 3.70 years. The present study is an attempt to validate the co-occurrence of metastatic prostate carcinoma and metabolic abnormalities leading to CVD and diabetes.

All the metastatic prostate carcinoma subjects included in the study were assessed for metabolic abnormalities as per ATP III and incidence of metabolic syndrome before they underwent through ADT as advised by the clinician or consultant (Table 1). There were 58.8% of patients with metastatic prostate carcinoma having metabolic syndrome while 4% of control subjects showed metabolic syndrome as per ATP III. This clearly reflects that the incidence of metabolic syndrome increases in subjects with metastatic prostate carcinoma. The difference in anthropometric measures in control and metastatic prostate carcinoma subjects was non-significant (table 1). However, the level of insulin was significantly (p=0.005) 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[25].

Further, in our study, the serum lipid profile level viz. TL, PL, TC, HDL, LDL, and VLDL in metastatic prostate carcinoma subjects and controls were comparable at baseline, except triglycerides which were significantly higher in subjects with metastatic prostate carcinoma. VLDL is also showed an increase over control values which show the positive correlation between increased dietary fat intake and higher incidence of prostate carcinoma.

Table:1
Anthropometric and biochemical parameters in controls and metastatic prostate carcinoma subjects before therapy

Parameters	Controls (25)	Subjects (51)	Statistical Correlation
BMI (kg/m2)	20.57 ± 1.04	20.90 ± 1.63	0.359
Waist circumference (cm)	89.16 ± 6.32	92.72 ± 4.58	0.007
Hip circumference (cm)	93.0 ± 6.27	95.31 ± 4.28	0.063
Waist: Hip ratio	0.957 ± 0.014	0.971 ± 0.013	0.000
Fasting plasma glucose (mg/dl)	90.88 ± 11.14	92.50 ± 13.27	0.601
Insulin (µU/ml)	3.33 ± 1.28	6.37 ± 2.36	0.000
Insulin Resistance	0.898 ± 0.547	1.46 ± 0.61	0.000
Insulin Sensitivity	0.647 ± 0.056	0.606 ± 0.08	0.024
Total Lipids (mg/dl)	492.72 ± 100.37	554.33 ± 101.25	0.015
Phospholipids (mg/dl)	144.68 ± 23.82	158.82 ± 37.75	0.091
Triglycerides (mg/dl)	72.92± 37.81	109.32 ± 31.83	0.000
Total cholesterol (mg/dl)	137.56± 27.74	143.23 ± 32.68	0.459
HDL (mg/dl)	47.12±6.26	44.98 ± 7.14	0.206
LDL (mg/dl)	75.85± 25.67	76.44 ± 30.82	0.934
VLDL (mg/dl)	14.58± 7.56	21.80 ± 6.36	0.000
Free fatty acids (mg/dl)	0.168± 0.045	0.189 ± 0.128	0.430
Testosterone (µU/ml)	581.92 ± 66.50	630.58 ± 190.42	0.220
PSA (ng/ml)	0.88 ± 0.33	89.80 ± 124.30	0.000
Prior Co morbidities			
Blood sugar (F)>110mg/dl	4	13	0.769
Triglycerides >150mg/dl	3	10	0.807
HDL-C<40 mg/dl	1	3	0.913
BP>130/80 mm/Hg	1	16	0.131
Waist circumference >102 cm	2	5	0.964
Metabolic syndrome			0.106
1 risk factor	4	18	
2 risk factors	2	7	
3 or more risk factors	1	5	
Zero risk factor	18	21	

Significant change: p= 0.000

BMI: body mass index, HDL: high density lipoproteins, LDL: low density lipoproteins, VLDL: very low density lipoproteins, PSA; prostate specific antigen, BP; blood pressure

The testosterone levels were found to be higher in subjects with metastatic prostate carcinoma as compared to controls. However, the difference was not found to be statistically significantat the baseline as prostate carcinoma has been recognized as an androgen-sensitive disease[2]. The prostate specific antigen is a known marker for prostate carcinoma and found to be significantly higher in prostate carcinoma subjects as compared to controls.

The study population was divided into two groups according to the type of ADT therapy given i.e. GnRH (n=18) and B/L orchiectomy (n=33) group. They were also examined for metabolic abnormalities before initiation of the treatment (Table-3).

Table2 is showing the comparison of various anthropometric and biochemical parameters before and after the ADT therapy of 12 and 18 months. A significant increase in WC was observed in subjects who have undergone treatment with ADT for 18 months. This indicates that ADT is associated with an increase in fat mass as androgens are important determinants of body composition and they promote lean body mass over fat mass. The biochemical parameters viz. fasting plasma glucose fasting, insulin and insulin resistance were significantly increased, and insulin sensitivity was significantly decreased in the group on GnRH therapy and group on B/L orchiectomy therapy. The results clearly indicate that ADT increases insulin resistance which plays a key role in the development of the metabolic syndrome. It also gives rise to impaired insulin sensitivity which increases the risk of diabetes, cardiovascular disease, myocardial infarction and sudden death. This is 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 which are the hallmarks of the insulin resistance found in metabolic syndrome.

Lipid profile and level of FFA after 12 and 18 months of therapy in GnRH and B/L orchiectomy groups were increased significantly. Since hyperlipidemia is a known metabolic risk factor for cardiovascular disease and is invariably associated with insulin resistance which is an important factor of metabolic syndrome. However, 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 subfraction. The findings of the present study indicate that the adverse metabolic profile observed in men who received ADT may be responsible for the higher risk of developing diabetes and cardiovascular disease in this population.

Level of testosterone and PSA decreased significantly in GnRH and B/L orchiectomy groups after 12 and 18 months of therapy. The basic premise or idea behind androgen deprivation therapy is to block the production or effects of androgens on the body by B/L orchiectomy or GnRH analogs and, thus, to slow or stop the growth of prostate carcinoma cells because androgens have been shown to cause prostate carcinoma cells to grow. The ADT reduces serum testosterone to anorchid levels within 12 hours, with rapid reduction of tumor burden in men with metastatic prostate carcinoma[2].

According to the Adult Treatment Panel-III criteria, a male is considered to have metabolic syndrome if he has three of the five criteria. Present study reveals that in the ADT group before therapy (Table 3) metabolic syndrome, one risk factor was found in 35% subjects , two risk factors, were found in 14% subjects, three risk factors were found in 10% subjects and no risk factor was found in 41% subjects. But after the therapy of 18 months, one risk factor was found in 10% of subjects, two risk factors were found in 20% subjects, three risk factors were found in 53% subjects and no risk factor was found in 10% of the subjects. This indicates that male hypogonadism is also acting as a risk factor in the development of the metabolic syndrome.

A significant negative correlation of IR, TG, and HDL level with testosterone level was observed in the study (Figure 1, 2 and 3 respectively). Therefore, the findings of the study indicate that hypogonadism itself leads to the development of insulin resistance and hyperglycemia and dyslipidemia which promotes angiogenesis. The present study indicates that there is a significant increase in metabolic syndrome risk factors in the subjects who have undergone ADT treatment (Table-3). Hence, it may be stated that ADT increases the metabolic burden. However, the level of HDL also increases significantly in the subjects receiving ADT therapy which is distinct from the classically defined metabolic syndrome.

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

Parameters	ADT (n=51)							
	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♯
Waist circumference (cm)	91.22± 4.70	94± 3.94	95.6± 4.07	.000**	93.54± 4.36	94.8± 4.86	98.15± 3.31	.005
Hip circumference (cm)	94± 4.41	95.61± 4.31	96± 4.21	.793	96.18± 4.44	96.45± 4.23	97.09± 4.97	.100
Waist:Hip ratio	0.970± 0.014	0.983± 0.014	0.997± 0.033	0.26	0.972± 0.013	0.983± 0.028	1.01± 0.045	.430
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	.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	.000***	0.591 ±0.053	0.478 ±0.036	0.453 ±0.040	0.000*
Total Lipids (mg/dl)	542.72± 123.96	795.94± 114.3	951.55± 301.72	.000♯	560.66± 87.96	881.36± 177.41	1025.57± 184.52	.000 **
Phospholipids (mg/dl)	163.8± 47.89	197.6± 33.22	247.61± 55.43	.000*	156.06± 31.41	235.66± 45.77	268.48± 35.41	.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 and 18 months was significant while change between baseline and12 months and 12 and 18 months was non-significant by post hoc test, ♯:change between baseline and after 12 months and18 months were significant, **:change between baseline, after 12 months and 18 months, between 12 and 18 months were significant

by post hoc test. ***:change between baseline and after 18 months and in between 12 and 18 months was significant by post hoc test.

Table:3

Prevalence of metabolic syndrome in the GnRH and B/L orchiectomy groups studied before and after 18 months of ADT therapy

Variables	ADT (n=51) Before therapy		p value	ADT (n=51) After therapy		p value
	GnRH (n=18)	B/L orchiectomy (n=33)		GnRH (n=18)	B/L orchiectomy (n=33)	
Prior Co morbidities						
Blood sugar (F)>110mg/dl	5	8	1.000	9	20	0.000*
Triglycerides >150mg/dl	5	5	0.220	10	20	0.000*
HDL-C<40 mg/dl	1	2	0.505	3	5	1.000
BP>130/80 mm/Hg	6	10	0.554	11	20	0.000*
Waist circumference >102 cm	0	5	0.711	3	7	0.503
Metabolic syndrome						
1 risk factor	7	11		3	4	
2 risk factors	2	5	0.266	3	7	0.092
3 or more risk factors	2	3		9	18	
Zero risk factor	7	14		3	4	

**Highly significant*

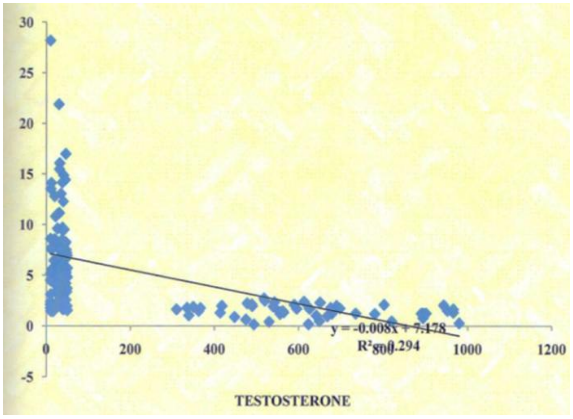

Figure 1: Correlation of Insulin Resistance with Testosterone in ADT Group during the Study Period

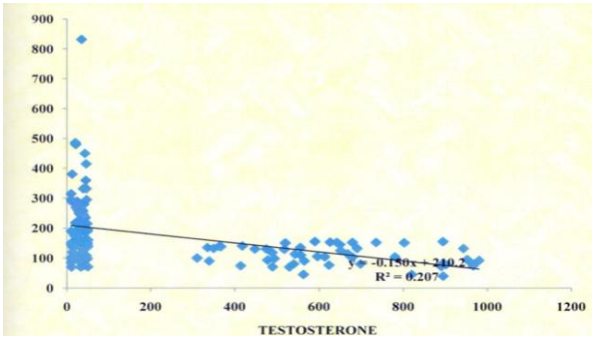

Figure 2:Correlation of Triglycerides with Testosterone in ADT Group during the Study Period

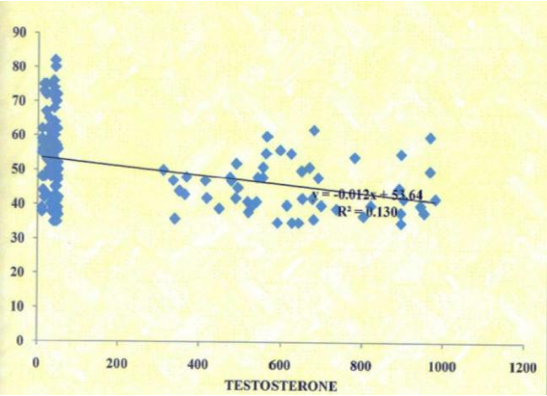

Figure 3:Correlation of HDL-Cholesterol with Testosterone in ADT Group during the Study Period

Conclusion:

The results of the present study suggest that the ADT adversely affects metabolic risk factors which are associated with insulin resistance, diabetes, and coronary artery disease. Thus, the subjects receiving ADT should be routinely assessed for metabolic abnormalities developed during the course of treatment, so as to prevent the development of diabetes and cardiovascular disease.

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Conflict of Interest Statement-

There is no conflict of interest.

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