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ORIGINAL ARTICLE

METABOLIC DISORDERS IN PATIENTS WITH DRUG-INDUCED HYPOGONADISM

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Abstract. Introduction: *Prostate cancer is among the most common types of cancer in men. Androgen deprivation therapy (ADT) has become one of the main treatment modalities, leading to drug-induced hypogonadism. Although male hypogonadism is recognized as a risk factor for the development of metabolic syndrome, the influence of ADT on metabolic parameters in prostate cancer patients has not been fully investigated. The aim of the present study was to analyze metabolic disturbances in prostate cancer patients on ADT and compare them with healthy controls.* ***Materials and Methods:*** *A cross-sectional study was performed between October 2022 and March 2024 investigating anthropometric parameters, blood pressure, fasting glucose, fasting insulin, total cholesterol, triglycerides, LDL- and HDL-cholesterol in prostate cancer patients on ADT (n=28) and healthy men (n=18).* ***Results:*** *At a similar age (67.5±8.5 years in prostate cancer patients and 65.6±8.6 years in controls), a significantly higher weight (93.7±8.1 kg vs 79.0±6.5 kg) and body mass index (31.38±4.86 kg/m^2 vs 27.70±2.83 kg/m^2) was observed among patients with prostate cancer compared to healthy men. Mean waist circumference of patients on ADT was 113.1±12.5 cm, significantly exceeding mean waist of the controls – 102.2±9.1 cm, (p<0.005). Higher triglyceride levels (2.11±1.75 mmol/l) were found in the patient group compared to controls (1.37±0.84 mmol/l), as well as lower HDL levels (1.41±0.38 mmol/l in patients on ADT vs 1.50±0.27 mmol/l in healthy men), both with borderline statistical significance. There was no statistically significant difference in total cholesterol and LDL-cholesterol value. There was an inverse relationship between serum testosterone and some anthropometric parameters such as: body weight (r -0.506; p<0.01); BMI (r -0.46; p<0.01); waist circumference (r -0.433; p<0.01). We also found inverse correlations of testosterone level with that of fasting glucose (r -0.479; p<0.01) and HOMA-IR (r -0.444; p<0.01). No significant differences in blood pressure values between patients and healthy controls were registered.* ***Conclusion:*** *Our results confirm the metabolic risk and highlight the need for investigation, follow-up and timely treatment of metabolic disturbances, especially lipid and carbohydrate disorders in men with prostate cancer undergoing hormone therapy.*

Key words: *prostate cancer, androgen deprivation therapy, hypogonadism, metabolic syndrome*

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INTRODUCTION

The United Nations 2023 report predicts doubling the number of people over 65 years between 2021 and 2050, and an even faster growth rate is expected for those over 80 years [1]. This will inevitably lead to a rise in chronic conditions, as well as some types of cancer, typical for this part of the population.

Because of the opportunistic use of various imaging modalities, there is now a massive improvement in the diagnosis of indolent tumors, including prostate cancer in men [2]. The latter is one of the most common neoplasms in men over 50 years of age. Since the discovery of the effect of castration (surgical or drug-induced) on prostate carcinoma by the Nobel laureate Dr. Charles Huggins in 1941, androgen deprivation therapy (ADT) has become one of the mainstay therapies [3, 4]. ADT not only reduces the risk of future recurrences, but also prolongs patients' lives [5]. According to an international survey of oncologists from 19 different countries around the world, following 99 177 cancer patients, the rate of prescription of ADT for those with non-metastatic prostate cancer was 38% [6]. According to another retrospective study in the USA 108 185 men were diagnosed with prostate cancer between 2004 and 2016, and 41.09% of them started ADT [7]. Therefore, a significant proportion of patients with prostate cancer will undergo treatment with ADT.

Currently, ADT is most commonly prescribed using LH-RH agonists (luteinizing hormone-releasing hormone agonists) like leuprolide, goserelin, and triptorelin, administered as a depot intramuscular or subcutaneous injection [3]. Their mechanism of action is based on stimulation of the LH-RH receptor located in the pituitary gland with subsequent release of LH (luteinizing hormone) further acting on the testicular Leydig cells, causing a temporary stimulation in testosterone secretion that activates the negative feedback loop in the pituitary gland with a subsequent decrease in male sex hormone levels within 4-6 weeks [3]. With the development of anti-androgens achieving complete androgen blockade, further improving the treatment of prostate cancer can be achieved with up to 90% therapeutic efficacy [2].

It is well known that hypogonadism is a risk factor for the development of metabolic syndrome, but the influence of ADT on metabolic markers in patients with prostate cancer has not yet been fully elucidated. Several population-based studies have already confirmed that testosterone levels below lower reference range are an independent risk factor for the development of diabetes mellitus and metabolic syndrome in men [8, 9, 10]. These observations are particularly important given the nearly 10-fold increase in the incidence of patients initiating ADT treatment in recent years worldwide [11]. It is also not surprising that among patients with prostate cancer, cardiovascular disease is the most common cause of death [12]. Therefore, knowledge of metabolic complications due to ADT is an important part of the overall treatment plan and choosing the appropriate mechanism to incorporate countermeasures to combat them.

The aim of this study was to analyze and compare anthropometric measures, as well as parameters of the carbohydrate and lipid metabolism in men with androgen deprivation therapy for prostate cancer and healthy controls.

MATERIALS AND METHODS

A cross-sectional study was performed between October 2022 and March 2024 investigating anthropometric parameters, blood pressure, fasting glucose, fasting insulin, total cholesterol, triglycerides, LDL- and HDL-cholesterol in prostate cancer patients on ADT (n=28) and healthy men (n=18).

Statistical analysis

Descriptive statistics, Mann-Whitney comparison of means, Spearman correlation coefficient were used to analyze the results.

RESULTS

At a similar age (67.5±8.5 years in patients and 65.6±8.6 years in controls), a higher body mass index (31.38±4.86 kg/m^2) was observed in the patient group compared to healthy men (27.70±2.83 kg/m^2) (Figure 1).

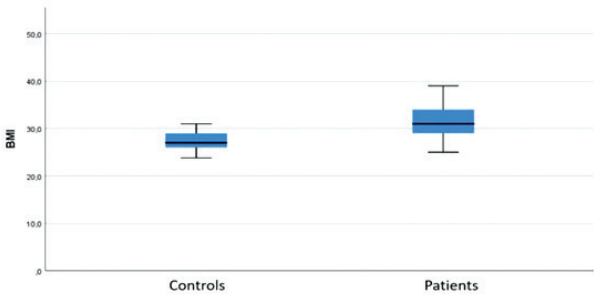

Fig. 1. Mean body mass index (BMI) in healthy controls (27.70±2.83 kg/m^2) and patients on ADT for prostate cancer (31.38±4.86 kg/m^2)

The difference in body weight between the two groups was also statistically significant with mean body weight in the patient group 93.7±8.1 kg (95% CI 86.7-100.78 kg) compared to 79.0±6.5 kg (95% CI 72.8-85.1 kg) in the control group, (p<0.005). Mean waist circumference of patients on ADT was 113.1±12.5 cm (95% CI 89-154 cm) significantly exceeding mean waist of the controls – 102.2±9.1 cm (CI 84-120 cm), (p<0.005).

The mean testosterone level of the healthy men was 14.30±4.38 nmol/l, whereas all the patients treated with ADT for prostate cancer had serum testosterone level ≤ 0.69 nmol/l, under limit detection of the measurement kit, as expected based on the ADT. Higher triglyceride levels (2.11±1.75 mmol/l) were found in the patient group compared to controls (1.37±0.84 mmol/l) (Figure 2). Mean HDL-cholesterol value of the patient group (1.41±0.38 mmol/l) was lower than the mean HDL-cholesterol value of the healthy controls (1.50±0.27 mmol/l) (Figure 3), with borderline statistical significance. There were no significant differences in total cholesterol (mean values 5.31±1.92 mmol/l for patients vs 5.14±0.87 mmol/l for controls) and LDL-cholesterol levels (2.88±1.77 mmol/l for patients vs 3.08±0.79 mmol/l for controls). We did not find any significant differences in blood pressure values between the two study groups (mean systolic pressure 138±15mmHg vs 135±14 mmHg; mean diastolic pressure 93±5mmHg vs 91±5 mmHg).

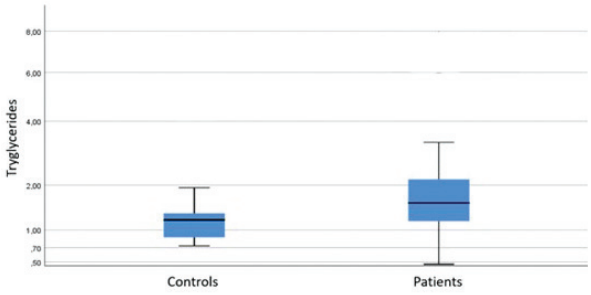

Fig. 2. Mean serum triglyceride levels in healthy controls (1.37±0.84 mmol/l) and in patients on ADT for prostate cancer (2.11±1.75 mmol/l)

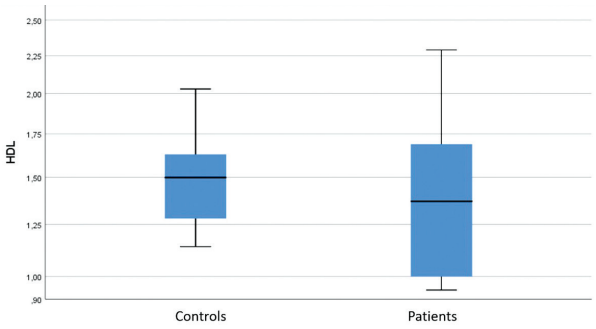

Fig. 3. Mean serum HDL-cholesterol levels in healthy controls (1.50±0.27 mmol/l) and in patients on ADT for prostate cancer (1.41±0.38 mmol/l)

Our results demonstrated an inverse relationship between testosterone levels and some anthropometric parameters such as: body weight (r -0.506; p<0.01) (figure 4); BMI (r -0.461; p<0.01) and waist circumference (r -0.433; p<0.01).

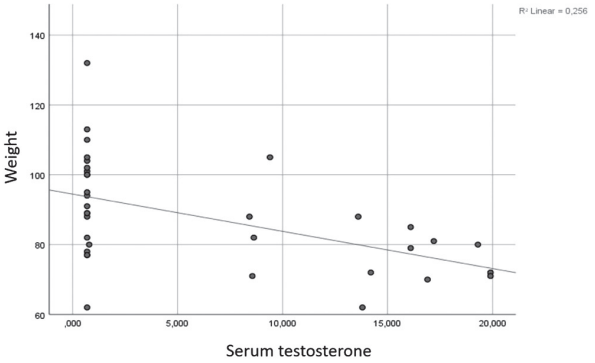

Fig. 4. Inverse correlation between serum testosterone and body weight

The analysis showed also inverse correlations of testosterone level with that of fasting blood glucose (r -0.479; p<0.01) (Figure 5) and HOMA-IR (r -0.444; p<0.01). Mean plasma fasting glucose in the patients group was 6.74 mmol/l (95% CI 6.2-7.2 mmol/l) and 5.6 mmol/l among healthy controls (95% CI 5.3-5.9 mmol/l), respectively. Another metabolic parameter, HOMA-IR was significantly increased among men on ADT – mean 11.7 (95% CI 1.92-21.6) compared to healthy controls – mean 4.24 (95% CI 0.7-7.7).

In our study, we found that metabolic syndrome was present among 92.9% (26 out of 28) of the patient group versus 44.4% (8 out of 18) of the control group by covering at least three criteria for its diagnosis.

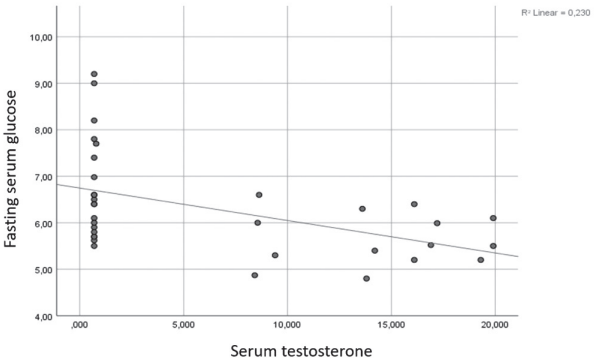

Fig. 5. Inverse correlations of testosterone level with that of fasting glucose

DISCUSSION

In our study, we observed that ADT is associated with an increase in body mass index and body

weight. Multiple other studies in patients with ADT also confirm that testosterone deficiency contributes to obesity [13, 14]. A cross-sectional study showed that men undergoing long-term ADT (12-101 months) accumulate an increased amount of fat in the trunk and limbs (documented by DEXA body composition analysis) compared with eugonadal men with prostate cancer [15]. Testosterone plays an important role in the regulation of body composition, performing various functions at the molecular level. It acts primarily as an anabolic hormone for the development of muscle mass and strength. In addition, testosterone can suppress adipocyte differentiation while promoting myocyte development by influencing their common precursor cells [16, 17]. Male hypogonadism of any nature results in a reduction in lean muscle mass and an increase in fat mass that is reversible with testosterone replacement therapy [18]. Even a short three-month course of ADT results in changes in body composition, increasing fat mass by +1.7 kg with a concomitant reduction in lean muscle mass of -1.7 kg [19]. These findings have been further confirmed by long-term prospective studies, one of which following a similar to our group of 40 patients on ADT for 48 weeks [20, 21]. During follow-up, both weight and BMI increased by 2.4% (p=0.005), and fat mass measured by DEXA increased by 9.4%, while lean muscle mass decreased by 2.7%. Abdominal circumference was increased by 3.9%, and it is interesting to note that this adipose deposition was at the expense of subcutaneous fat rather than visceral fat.

Smith et al. published similar observations in a group of 88 patients treated for 48 weeks with ADT using computed tomography as the imaging modality and reported 11% increase in subcutaneous adipose tissue, with no significant changes in visceral adipose tissue [22]. Furthermore, the mean reduction in muscle mass among different studies after 1 year was between 2.2% and 3.8%, depending on the drug used in ADT. The resulting changes in body composition, manifested by a decrease in lean mass and an increase in adipose tissue, termed sarcopenic obesity, is widespread among patients with prostate cancer on ADT. The increase in adipose tissue is connected with higher insulin levels, insulin resistance and a chronic state of inflammation. On the other hand, sarcopenia further contributes to reduced glucose utilization and the manifestation of metabolic syndrome.

Metabolic syndrome is defined by a cluster of interconnected risk factors specific to cardiovascular diseases and diabetes type 2 [23]. Diagnosis is based on fulfilling three out of five criteria. For Caucasian men these are: waist circumference >94 cm, serum triglyceride levels above 1.7 nmol/L or use of medication for hypertriglyceridemia, HDL-levels below 1.3 mmol/L or use of lipid-lowering medication, blood pressure above 130/85 mmHg or use of antihypertensive medication, and fasting blood glucose above 5.6 mmol/L or treatment with glucose-lowering medication [23].

In our cohort we found very high prevalence of metabolic syndrome among ADT treated patients (92.9%) but also among the controls (44.4%). These results are associated with the mean age exceeding 65 years, as well as the high prevalence of metabolic syndrome in Bulgarian population per se. In comparison, an epidemiological study of Gleicher et al. over 9000 men aged 20-59 years found that men with hypogonadism had a significantly higher prevalence of metabolic syndrome – 36.5% compared to 20% among men with normal testosterone ($p<0.001$) [24]. According to this study, the increase of waist circumference and the decrease in HDL-levels significantly increased the chance of men having low testosterone levels (OR 4.32, 95% CI 2.51-7.45, $p<0.001$ and OR 1.67, 95% CI 1.15-2.41, $p=0.008$, respectively) [23]. Cross-sectional studies showed that the incidence of metabolic syndrome was higher among men with hypogonadism, even after removing secondary factors [25].

Depending on the duration of ADT, patients with prostate cancer are at high risk of developing metabolic syndrome [26]. Prospective studies have also highlighted some specific differences in the presentation of metabolic syndrome among patients on ADT, compared to the “classic” variant. For example, in patients with prostate cancer and hypogonadism, there is no change in waist-to-hip ratio and similarly with our findings no change in blood pressure [26, 27]. Some authors do not register diminished HDL-cholesterol levels [26, 27]. However, it is not clear whether these differences lead to different clinical complications.

In recent years, much evidence has been accumulated that low testosterone levels may be associated with development of insulin resistance and type 2 diabetes mellitus in men [28, 29]. Tsai et al. observed an inverse correlation between testosterone levels and insulin resistance [30]. Furthermore, interventional studies reported improvement in insulin sensitivity with testosterone replacement therapy in hypogonadal men [31]. A meta-analysis including 1596 hypogonadal men with type 2 diabetes mellitus from 12 randomized-controlled and one observational study showed that testosterone replacement therapy improved glycemic control, fasting insulin levels and lipid parameters compared to placebo [32].

A cross-sectional study of Basaria et al. involved 53 men, 18 undergoing ADT for a 1-year period (ADT

group), 17 eugonadal men with prostate cancer of similar age (Non-ADT group), and 18 healthy male controls [33]. The results showed that patients undergoing ADT had significantly higher insulin levels, a higher incidence of insulin resistance compared with the other two groups. The key finding was that more than 44% of the ADT group met the criteria for a diagnosis of diabetes mellitus compared with 12% and 11% versus the non-ADT group and the control group, respectively. Men on hormonal therapy also had higher leptin levels, reflecting increased adipose tissue mass.

Insulin resistance leading to prediabetes and diabetes type 2 is also a predictor of coronary heart disease and stroke [34, 35, 36]. Several studies have shown that even a relatively short ADT of 6 months increases the risk for diabetes, cardiovascular disease, and myocardial infarction [37]. This cardiovascular risk may partially be connected with the pharmacological side effects of some of the drugs, exhibiting proarrhythmic risk [38]. Meta-analyses of observational studies highlight the association between ADT and the risk of cardiovascular disease in patients treated for prostate cancer [39]. For example, LH-RH agonists therapy is associated with a relative risk for nonfatal myocardial infarction of 1.57 (95% CI: 1.26-1.94) and for stroke – RR 1.51 (95% CI 1.24-1.84).

Another retrospective analysis found associations between ADT and increased cardiovascular mortality, newly diagnosed congestive heart failure, and survived myocardial infarction [40, 41]. It has been suggested that the use of injectable LH-RH antagonists could reduce these risks compared with agonists, but there is not yet sufficient evidence to support these claims [42, 43]. In a phase III randomized controlled trial with a follow-up period of 48 weeks, treatment with an oral LH-RH antagonist (relugolix) was associated with a reduced risk of a major cardiovascular event compared with an injectable LH-RH agonist (leuprolide), 2.9% versus 6.2%, respectively [44].

Independently of the androgen deprivation agent, it seems reasonable to follow up patients undergoing long-term treatment with ADT and to determine whether the metabolic disorders worsen or remain stable with time. Preventive measures to counteract adverse outcomes include nonspecific approaches such as weight loss, increased physical activity, minimizing alcohol consumption, healthy diet, and smoking cessation [45, 46]. Additionally to these lifestyle changes, metformin may reduce the metabolic complications of androgen suppression in men with prostate cancer [46].

CONCLUSION

Our initial results on a small number cohort highlight the need for investigation, follow-up and timely treatment of metabolic disturbances, especially lipid and carbohydrate disorders in men with prostate cancer undergoing hormone therapy.

Conflict of Interest Statement: *The authors declare no conflicts of interest related to this work.*

Funding: *The authors did not receive any financial support from any organization for this research work.*

Ethical statement: *This study has been performed in accordance with the ethical standards as laid down in the Declaration of Helsinki. The research was approved by local Ethics Committee of Medical University of Varna.*

Informed Consent from Participants: *Informed consent was obtained from all participants included in the study.*

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