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Metabolic Complications of Androgen Deprivation Therapy for the Treatment of Prostate Cancer

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Abstract

Aim: Prostate cancer is the most commonly diagnosed cancer and second leading cause of cancer death in U.S. men. The b median age at diagnosis is 67 years, with black men having a 50% higher risk of developing prostate cancer and two-fold mortality rate compared with Caucasians. The use of androgen deprivation therapy (ADT) is associated with symptom control in patients with metastatic prostate cancer but no known survival advantage. This therapy has significant impact on skeletal health, but more recently, the metabolic complications of ADT have been recognized. These include obesity, insulin resistance, diabetes, lipid alterations and cardiovascular health, which will be the focus of this review.

Method: We performed a PubMed search (1950-2014) of articles written in English using search terms including prostate cancer, androgen deprivation therapy, gonadotropin-releasing hormone agonists, insulin resistance, diabetes, and cardiovascular disease.

Result: Due to the general indolence of prostate cancer in older men, many will live with the consequences of cancer-related treatment, particularly the acquired hypogonadism related to use of ADT. Androgen deprivation therapy decreases lean mass and increases fat mass. It also decreases insulin sensitivity while increasing low density lipoprotein cholesterol, high density lipoprotein cholesterol and triglycerides. These translate to greater incidence of diabetes, cardiovascular and skeletal disease.

Conclusion: Approximately 33-70% of men with prostate cancer will undergo treatment with ADT at some point in the treatment of their disease. Hence, it is important for physicians and patients to consider the metabolic consequences such as risk of diabetes and cardiovascular disease, and balance it against the potential benefits of therapy when making treatment decisions about ADT. In the absence of high level evidence, we recommend following well established guidelines on screening, prevention and management of these effects as in the general population.

Keywords: Androgen deprivation therapy; Gonadotropin releasing hormone; Prostate specific antigen; Oral glucose tolerance test; Hypogonadism; Dyslipidemia; American diabetes association

Introduction

Prostate cancer is the most commonly diagnosed cancer and second leading cause of cancer death in U.S. men [1]. In 2010 National cancer statistics showed 196,038 men in the United States were diagnosed with prostate cancer and 28,560 deaths occurred [2]. The median age at diagnosis is 67 years, and over 8% of men will develop cancer of the prostate between the ages of 50 and 70 years [3]. Black men have a 50% higher risk of developing prostate cancer and two-fold mortality rate compared with white men [2]. With the introduction of prostate-specific antigen (PSA) screening, most men are diagnosed with localized disease; <10% have locally advanced and 30% have metastatic disease at initial diagnosis. The use of androgen deprivation therapy (ADT) has improved symptom control for patients with metastatic prostate cancer, but no survival advantage has been conclusively demonstrated in these patients [3].

Approximately, 70% of prostate cancers are androgen-dependent [4] and respond to some form of hormonal ablation therapy, which diminishes testosterone exposure, a growth factor for prostate cancer [5]. Androgen deprivation therapy (ADT) will suppress testosterone production from the testes to castrate levels, leading to hypogonadism. Castration can be achieved medically with the use of Gonadotropin-Releasing Hormone Agonists (GnRH-agonists), and/or anti-androgen medications or surgically with bilateral orchiectomy. The latter is less common because of irreversibility; however, may be chosen in men who are hypogonadal at diagnosis [6]. Anti-androgens such as biclutamide and flutamide are competitive inhibitors of the androgen receptor, blocking testosterone action at the prostate and are typically used in conjunction with GnRH-agonists or less often as monotherapy [7]. Estrogen preparations were used historically to achieve castration, but have been much less favored because of their association with thromboembolic phenomena and adverse events [8].

Approximately 33-70% of men with prostate cancer now receive ADT as primary therapy [8] before and after definitive surgery or radiotherapy for localized disease. In patients with locally advanced disease as well as those with high-risk localized disease (based on tumor stage, Gleason score and PSA), neoadjuvant therapy is

considered standard of care as studies have shown benefit regarding disease-specific survival, time to progression and all-cause mortality [9]. In the adjuvant setting, ADT for >2 years given in conjunction with external-beam radiotherapy in men with locally advanced, high-risk prostate cancer has been demonstrated in major prospective, randomized trials to improve survival in this population [10].

As prostate cancer is most often a disease of older men, 50% over age 75 years will have other co-morbidities. Due to the general indolence of prostate cancer in older men, many will live with the consequences of cancer-related treatment, particularly the acquired hypogonadism related to use of ADT. This therapy has significant impact on bone health including decreased bone density, decreased muscle mass [11], increased fall risk and impaired balance [12]. More recently the metabolic complications of this therapy including obesity, insulin resistance, diabetes, lipid alterations and its effect on cardiovascular health have been documented, and will be the focus of this review.

Body Composition Changes with Androgen Deprivation Therapy

Obesity is currently a worldwide epidemic [13,14]; therefore, the effects of ADT on body composition are important to understand. Androgens are major determinants of body composition as they promote lean body mass over fat mass [15]. This can be therapeutically useful, as exogenous testosterone replacement increases lean body mass in men who are hypogonadal due to medical comorbidities [13,14]. Conversely ADT increases fat mass and decreases lean body mass [16].Sarcopenic obesity is a relatively new term used to describe weight gain with decrease in muscle mass and strength [17] as is seenin men with prostate cancer treated with ADT.

A number of prospective studies have examined ADT induced changes in body composition in the first year of therapy. Overall, these studies have demonstrated weight increase of about 1.8-2.4 % ± 0.8%, (p=0.005), increase in percentage of body fat mass of 9.4-11.2% ± 0.5%, (p<0.001), and decrease in lean mass 2.7-3.8% ± 1.5%, (p<0.001) measured by bioelectrical impedance analysis and dual-energy x-ray absorptiometry [18-25].Most prospective studies have shown that this is an early complication apparent in first 3 months. In fact, one study showed that receiving ADT for a prolonged period (greater than 12 months) predicted smaller changes in body composition [26,27] emphasizing the dynamic changes early in treatment.

Two prospective studies report fat accumulation during treatment with GnRH agonists is primarily subcutaneous fat, while intra-abdominal or visceral fat generally does not change significantly [28,29]. In one report, subcutaneous fat accounted for 94% of the observed 16.5% +/-2.6%, increase in total abdominal fat area (p-0.001) by cross sectional imaging [30].

In summary, ADT is associated with body composition changes which include increase in subcutaneous fat but no significant change in the visceral fat, which is most apparent in the first 3 months. Studies are limited regarding prevention of these body composition changes. Resistance exercise promotes muscular fitness, less fatigue, and higher quality of life as described in one study of men randomized to resistance exercise 3 times a week compared with controls not actively exercising [31], but no significant difference in body composition was seen after 3 months of ADT.

Lipid Alterations

Evidence from several short-term prospective studies has demonstrated inconsistent adverse effects of GnRH agonists on lipids. In a prospective study of 26 men receiving ADT for 24 weeks, Eri et al. [32-35]documented increased total cholesterol (10.6%, P-0.005) HDL, (8.2%, p-0.002) and triglycerides without change in low-density lipoprotein [36]. In contrast, Dockery et al. [37] reported increase in HDL and total cholesterol, but no significant adverse changes in triglycerides, low-density lipoprotein, or serum glucose levels among 15 men receiving ADT when evaluated at three months (p value<0.005). Another study by Smith et al. [38-40] noted increased total cholesterol, LDL, HDL, and triglycerides in 40 men ($p \leq 0.02$) with locally advanced or recurrent prostate cancer receiving ADT in a 48-week prospective study [41].

Yannucci et al. compared fasting serum lipids, glucose levels, and glycosylated hemoglobin at baseline, days 85 and 169 in 1,102 men receiving abarelix (a GnRH antagonist not approved in US), leuprolide acetate (GnRH agonist), or leuprolide plus an anti-androgen, bicalutamide. Decrease in triglycerides was observed in those receiving leuprolide plus bicalutamide (total androgen blockade) while significant increase in total cholesterol, triglyceride, LDL-C and HDL was noted in the abarelix and leuprolide group. The increases in total cholesterol occurred concomitantly with increase HDL during the first 6 months of ADT, mitigating the consequence of increased total cholesterol. In this study, significant increases in non-HDL cholesterol were only observed in patients on abarelix [24]. In a prior study in men with no prostatic cancer, GnRH agonist treatment was shown to increase HDL-C [25]. These observations suggest that it is possible that GnRH antagonists and GnRH agonists have different effects on HDL-C. Whether an increased HDL in men on ADT suggests any protective effect is currently unknown.

In summary, most studies have described increases in cholesterol and HDL, but variable effects, ranging from no significant change to increases in LDL-C and triglycerides. A small number of studies have described the positive effect of exercise on weight gain, BMI, abdominal girth, upper and lower body fitness and quality of life [26]. The major challenge in this area of research is motivating subjects to stay on exercise programs for a sufficient duration of time, so that true impact could be determined. Hence, awareness of these potential changes and management strategies for them prompts setting up goals at the beginning of treatment with ADT which may translate to reduction in cardiovascular risks.

Insulin Resistance

Insulin resistance is a metabolic disturbance that includes diabetes, prediabetes and obesity. It is also an independent risk factor for coronary artery disease [27,28]. Insulin resistance in response to GnRH agonists is an early development and also a risk factor for DM, CAD, and sudden cardiac death [29].

Early prospective studies have shown increases in fasting insulin in response to ADT treatment. In a 3-month study of 16 men initiating GnRH agonist treatment, Dockery et al showed that fasting insulin levels nearly doubled from 6.89 (±4.84) mU/Lto11.34 (±8.16) mU/L with no significant change in glucose levels and BMI [23]. In a prospective study of 25 men receiving GnRH agonist and bicalutamide therapy for 12 weeks, Smith et al showed a significant 13% decrease (p-0.02) in insulin sensitivity index by the oral glucose tolerance test [29]. Conversely, fasting plasma insulin levels increased significantly

by 26% (p-0.04) and mean glycosylated hemoglobin increased slightly from 5.46 to 5.62 ± 0.09 (P<0.001), and one of the 25 subjects met criteria for diabetes mellitus at the week 12 OGTT [29].

In summary, there is decrease in insulin sensitivity, and an increase in insulin and HbA1cin patients on ADT. There are no specific recommendations for management of insulin resistance in the setting of ADT treatment in prostate cancer; however, general ADA recommendations include weight loss of at least 10-15% of body weight and physical exercise of about 30 minutes at least 5 times a week in patients with impaired fasting glucose [30].

Diabetes

Insulin sensitivity is known to decrease as BMI increases; hence, obesity and insulin resistance are strongly associated with diabetes [31]. In a large observational study by Keating et al followed 73,196 men over 65 years diagnosed with prostate cancer between 1992 to 1999 with a mean follow-up of 3 years. The investigators analyzed the potential relationship between ADT and the new diagnosis of diabetes using the SEER and Medicaid data base. Among one third of the men on GnRH agonists, there was a 44% increased risk of diabetes (HR-1.44, p<0.001) compared with men with prostate cancer not receiving ADT. Similarly, the 7% who underwent orchiectomy were also more likely to have diabetes (Hazard ratio-1.34) [30]. In a further study of more than 37,000 veterans, the same investigators found a 28% increased risk of incident diabetes in men receiving GnRH-agonists [32].

Although hypogonadism is not usually considered a risk factor for diabetes, it is recommended, based on recent data on ADT and insulin sensitivity [42-48] to treat all patients on ADT as high risk patients with close follow-up.

Cardiovascular Morbidity and Mortality

The possible association between GnRH agonists and cardiovascular morbidity and mortality has been the subject of several analyses. As ADT is associated with obesity, insulin resistance and dyslipidemia, potential increased risk for cardiovascular disease is of concern. Keating et al. [30] assessed the relationship between ADT and new cardiovascular disease and found that men who received GnRH agonists had a higher incidence of coronary heart disease (HR-1.16, p<0.001), myocardial infarction (HR-1.11, p-0.03) and ventricular arrhythmia/sudden cardiac death (HR-1.16, P-0.004) compared with men with prostate cancer not receiving ADT. Interestingly, this risk of excess events was not seen with orchiectomy, raising the possibility that the events could be related to the GnRH agonists themselves, although relatively few men underwent orchiectomy.

In another retrospective study of 23,000 men with prostate cancer, ADT increased the risk of serious cardiovascular morbidity by 20% at 1 year [35]. Further retrospective data from the Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) registry suggested that among men >65 yr of age receiving radical prostatectomy, those who also received ADT had a significantly higher risk of fatal CV events. In a large meta-analysis, it was found that statins, in addition to life style modification and exercise, were the main pharmacological treatment found to reduce all-cause mortality by approximately 16% in a prostate cancer population [49,50].

These studies led to a science advisory jointly released in 2010 by the American Urological Association, the AHA, American Cancer Society, and American Society of Radiation Oncologists stating that “at this point, it is reasonable, on the basis of the above data, to state that there may be a relation between ADT and cardiovascular events and death”. That same year, the FDA issued a drug safety communication requiring manufacturers of GnRH agonists to modify their labeling to warn of an “increased risk of diabetes and certain cardiovascular diseases (heart attack, sudden cardiac death, and stroke)” [28].

Several large radiation therapy oncology group (RTOG) trials have shown comparable cardiovascular mortality regardless of ADT assignment. In RTOG 92-02, 1,554 men with locally advanced prostate cancer were randomized to radiation with 4 or 28 months of ADT using GnRH agonist [43]. The five year cardiovascular mortality was 5.9% with long duration and 8.4% with short duration ADT, a non-significant difference. RTOG 85-31 compared radiation alone to radiation with indefinite ADT in a group of more than 900 men with prostate cancer and unfavorable prognoses due to T3 tumors or nodal involvement [33,42]. Cardiovascular mortality was 8.4% with indefinite ADT and 11.4% when ADT was started only on evidence of recurrence, non-significant differences. The absence of a significant difference between treatment groups in this trial suggests no increase in cardiovascular mortality risk with increasing duration of GnRH agonist treatment in these studies [30,33].

Although most studies demonstrate an association between ADT and cardiovascular events, there is no definitive evidence that ADT is associated with greater cardiovascular mortality. Cardiovascular risk factors are complex with many contributing factors, and these studies were carried out in different populations with a small number of actual cardiovascular events. Thus, they may have been underpowered to detect meaningful changes. Although studies have suggested an increased risk, longer prospective follow-up in larger cohorts would be needed to further determine whether causal relationships exist between ADT and cardiovascular morbidity and mortality.

Conclusion

Currently, PSA measurement has led to earlier diagnosis of localized prostate cancer in many men, and thus more widespread use of GnRH- agonists. These agents, widely used for the treatment of prostate cancer, are associated with several metabolic changes including obesity, insulin resistance, lipid alterations, increased risk of diabetes and cardiovascular events. Diabetes and cardiovascular disease are among the leading causes of non-cancer death in men with prostate cancer, accounting for about 35% of deaths in one analysis [11]. Therefore, it is important to detect and manage these metabolic changes. In the absence of high level evidence specific to this population, we recommend following well established guidelines on screening and management in the general population.

Physicians and patients should consider the metabolic side effects, risk of diabetes and cardiovascular disease when making treatment decisions about ADT. Clinicians should educate patients about these risks as they must be balanced against the potential benefits of therapy. It is reasonable to adopt strategies to decrease the risk of diabetes and cardiovascular disease. These include screening for prediabetes and/or diabetes, lifestyle modifications according to ADA guidelines and management of lipids according to NCEP ATP III guidelines even before initiation of ADT [27]. Finally, physicians and patients alike should support survivorship research to further our understanding and improve our management of these important issues.

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