Special Article

Metabolic Complications of Androgen Deprivation Therapy for Prostate Cancer

Philip J. Saylor* and Matthew R. Smith†

From the Department of Oncology, Massachusetts General Hospital Cancer Center, Boston, Massachusetts

Abbreviations and Acronyms

ADA = American Diabetes Association
ADT = androgen deprivation therapy
AHR = adjusted hazard ratio
BMI = body mass index
CaPSURE = Cancer of the Prostate Strategic Urologic Research Endeavor
CHD = coronary heart disease
CV = cardiovascular
EORTC = European Organization for the Research and Treatment of Cancer
FPG = fasting plasma glucose
GnRH = gonadotropin-releasing hormone
HDL = high density lipoprotein
IFG = impaired fasting glucose
IGT = impaired glucose tolerance
LDL = low density lipoprotein
MI = myocardial infarction
NCEP ATP III = National Cholesterol Education Program Adult Treatment Panel III
OGTT = oral glucose tolerance test
PSA = prostate specific antigen
RT = radiation therapy
RTOG = Radiation Therapy Oncology Group
SCD = sudden cardiac death
SEER = Surveillance, Epidemiology and End Results

Purpose: Androgen deprivation therapy has a variety of well recognized adverse effects including vasomotor flushing, loss of libido, fatigue, gynecomastia, anemia and osteoporosis. This review focuses on the more recently described metabolic complications of androgen deprivation therapy including obesity, insulin resistance and lipid alterations as well as the association of androgen deprivation therapy with diabetes and cardiovascular disease.

Materials and Methods: We reviewed the medical literature using the PubMed® search terms prostate cancer, androgen deprivation therapy, gonadotropin-releasing hormone agonists, obesity, insulin resistance, lipids, diabetes, cardiovascular disease and myocardial infarction. We provide a focused review and our perspective on the relevant literature.

Results: 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. Consistent with these adverse metabolic effects, androgen deprivation therapy may be associated with a greater incidence of diabetes and cardiovascular disease. Some of these androgen deprivation therapy related metabolic changes (obesity, insulin resistance and increased triglycerides) overlap with features of the metabolic syndrome. However, in contrast to the metabolic syndrome, androgen deprivation therapy increases subcutaneous fat and high density lipoprotein cholesterol.

Conclusions: Androgen deprivation therapy increases obesity, decreases insulin sensitivity and adversely alters lipid profiles. It may be associated with a greater incidence of diabetes and cardiovascular disease. The benefits of androgen deprivation therapy should be weighed against these and other potential harms. Little is known about the optimal strategy to mitigate the adverse metabolic effects of androgen deprivation therapy. Thus, we recommend an emphasis on existing strategies for screening and treatment that have been documented to reduce the risk of diabetes and cardiovascular disease in the general population.

Key Words: prostatic neoplasms, gonadotropin-releasing hormone agonists, cardiovascular diseases, diabetes mellitus, obesity

Submitted for publication November 14, 2008.

* Correspondence: Department of Medical Oncology, Massachusetts General Hospital Cancer Center, 55 Fruit St., POB-2-221, Boston, Massachusetts 02114 (e-mail: psaylor@partners.org).

† Supported by a National Institutes of Health K24 Midcareer Investigator Award (5K24CA121990-02), and grants from the Prostate Cancer Foundation and Lance Armstrong Foundation.

For most men the diagnosis of prostate cancer does not alter life expectancy. The contemporary 5-year relative survival for men with all stages of prostate cancer combined is 98.8%.[1] With these improvements in prostate cancer specific survival, consideration of treatment related morbidity has become increasingly important.

ADT can be accomplished with surgical castration (bilateral orchiectomy) or medical castration with

0022-5347/13/1891-0034/0
THE JOURNAL OF UROLOGY®

http://dx.doi.org/10.1016/j.juro.2012.11.017
Vol. 189, S34-S44, January 2013
Printed in U.S.A.

Please cite this article as J Urol 2013;189: S34-S44. DOI: http://dx.doi.org/10.1016/j.juro.2012.11.017

GnRH agonist therapy and is an effective treatment for prostate cancer in a variety of clinical settings. GnRH agonists improve disease-free and overall survival when used in combination with primary radiation for locally advanced or high risk localized disease.[2,3] ADT alleviates bone pain and modestly prolongs survival when used for the palliation of metastatic disease.[4] GnRH agonists have largely replaced bilateral orchiectomy for a variety of reasons including ease of administration, reversibility, and the cosmetic and psychological issues associated with orchiectomy.

GnRH agonist use has increased steadily during the last 2 decades.[5,6] There is evidence for improved disease-free or overall survival for 1) the combination of GnRH agonist therapy with primary radiation for locally advanced or high risk disease[2,3] and 2) adjuvant therapy for pN1 disease after prostatectomy.[7] In addition, PSA monitoring after primary therapy for prostate cancer facilitates the detection of PSA recurrent disease long before such recurrences would have become clinically evident. PSA only recurrence after surgery or RT often leads to long-term ADT. Finally, some men opt for long-term ADT for localized disease as an alternative to radiation or surgery, an approach that has not been shown to improve survival compared to conservative management.[8]

Regardless of the indication GnRH agonist therapy produces a marked reduction in circulating testosterone and a number of associated changes. It is now known to cause detrimental changes in body composition, lipid profile and insulin sensitivity. GnRH agonists are also associated with greater risks of incident diabetes and cardiovascular disease. This review summarizes the evidence for these recently recognized metabolic complications of ADT, and discusses established and emerging strategies to prevent related morbidity.

OBESITY AND SARCOPENIA

Obesity is an epidemic worldwide. The World Health Organization estimates that worldwide more than 1.7 billion people are overweight (BMI between 25.0 and 29.9 kg/m^2) and 310 million are obese (BMI 30.0 kg/m^2 or greater). Rates of obesity in the developing world have tripled in the last 20 years.[9] Obesity is particularly prevalent in the United States and other Western countries. Approximately 72 million American adults, including 33.3% of men, were obese as of 2007.[10]

Androgens are important determinants of body composition as they promote lean body mass over fat mass.[11] This can be therapeutically useful as exogenous testosterone replacement increases lean body mass in men who are hypogonadal due to medical comorbidities such as age or HIV infection.[12,13]

Conversely ADT increases fat mass and decreases lean body mass.[14,15] Sarcopenic obesity is a relatively new term for the combination of excess weight and reduced muscle mass or strength.[16] One early prospective study examined ADT induced changes in body composition by following 40 men with locally advanced nonmetastatic prostate cancer from initiation through the first year of GnRH agonist therapy.[15] During 1 year weight increased by 2.4% ($\pm$0.8%, $p = 0.005$), percentage fat body mass increased by 9.4% ($\pm$1.7%, $p < 0.001$) and percentage lean body mass decreased by 2.7% ($\pm$0.5%, $p < 0.001$). Similarly a larger study of 79 men with nonmetastatic prostate cancer also showed significant weight gain (1.8% $\pm$ 0.5%, $p < 0.001$) during 1 year of ADT.[17] Percentage fat mass increased (11.0% $\pm$ 1.7%) and percentage lean mass decreased (3.8% $\pm$ 0.6%). Another prospective study of 26 men receiving 12 months of GnRH agonist therapy found that fat mass increased by 11.2% ($\pm$1.5%, $p < 0.001$) and lean body mass decreased by 3.6% ($\pm$0.5%, $p < 0.001$).[18]

Fat accumulation during treatment with GnRH agonists is primarily subcutaneous fat (fig. 1). In contrast, intra-abdominal fat generally does not change significantly. In 1 study subcutaneous fat area by cross-sectional imaging increased by 11.1% ($\pm$3.4%, $p = 0.003$) during the first year of ADT while intra-abdominal fat area did not change significantly.[15] In another report subcutaneous fat accounted for 94% of the observed 16.5% ($\pm$2.6%, $p < 0.001$) increase in abdominal fat area.[19]

Treatment related alterations in body composition are early adverse effects. Two studies have demonstrated significant changes within the first 3 months of therapy. In 1 study 3 months of ADT caused significant increases in fat mass and circulating insulin in 22 treatment naïve men.[20] In another study 12 weeks of combined androgen blockade with a GnRH agonist and bicalutamide in 25 men caused a 4.3% ($\pm$1.3%, $p = 0.002$) increase in fat body mass.[21] A prospective study of 65 men receiving 12 months of therapy demonstrated that a longer duration of previous treatment predicted smaller changes in body composition, highlighting the dynamic changes early in treatment.[22]

Little is known about the best strategy to prevent treatment related changes in body composition. One study randomized 155 men to 3 times per week resistance exercise or to a waiting list control group upon initiation of ADT. After 3 months of ADT, body composition did not differ between the groups.[23] The resistance training group did benefit from less fatigue, higher quality of life and higher levels of muscular fitness.