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How can we improve the health of men who receive ADT?

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Abstract

Clinical research in recent years has produced a deepening appreciation of the metabolic consequences of androgen deprivation therapy. On the basis of this knowledge, proactive management of risk factors for diabetes and cardiovascular events is appropriate in men who receive this treatment for prostate cancer.

The use of androgen deprivation therapy (ADT) for men with prostate cancer has risen such that more than one-third of the estimated 2 million prostate cancer survivors in the USA are currently treated with gonadotropin-releasing hormone (GnRH) agonists.[1] However, concerns about the metabolic and cardiovascular consequences of ADT have recently emerged. Prospective studies have shown that GnRH agonists cause a rise in total cholesterol and triglycerides, weight gain, and a decline in insulin sensitivity. Obesity and insulin resistance are both strongly associated with type 2 diabetes in the general population. This constellation of metabolic changes is also suggestive of an increased risk of heart disease in men who receive ADT. Diabetes and heart disease are among the leading causes of death in American men, and represent serious health care problems worldwide.

In an article published in the *Journal of Clinical Oncology*, Alibhai and colleagues[2] report the findings of a matched cohort study that investigated the effect of ADT on diabetes and cardiovascular morbidity using health care databases from Ontario, Canada. Their analysis included data from almost 20,000 men aged ≥66 years who were treated with either bilateral orchiectomy or at least 6 months of medical castration with GnRH agonists, nonsteroidal antiandrogens or steroidal antiandrogens. These patients were matched with men who had been diagnosed with prostate cancer but who had not received ADT. The investigators found an ADT-associated increase in the risk of diabetes (hazard ratio [HR] 1.16, 95% Ci 1.11–1.21), confirming earlier observations.[1] In contrast to earlier studies, however, they found no association between ADT and an increased risk of acute myocardial infarction (HR 0.91, 95% CI 0.84–1.00).

In previous work, Keating *et al.*[1] examined the Medicare records of 73,196 patients aged ≥66 years who had locoregional prostate cancer, and found that those patients treated with a GnRH agonist had a significantly increased risk for incident diabetes (HR 1.44), coronary heart disease (HR 1.16), myocardial infarction (HR 1.11), and ventricular arrhythmias or sudden cardiac death (HR 1.16). Using retrospective data from a population of almost 23,000 men with prostate cancer, Saigal *et al.*[3] similarly demonstrated a 20% ADT-associated rise in the risk of serious cardiovascular morbidity at 1 year. In a smaller cohort of 3,262 men who had undergone radical prostatectomy, retrospective analysis found a statistically significant association between

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neoadjuvant ADT and cardiovascular mortality among men aged ≥65 years (adjusted HR 2.6; $P = 0.002$).[4] Limitations of this analysis include the small number of events (61 deaths among included men) and failure to validate well-described risk factors for cardiovascular death (for example, baseline diabetes and coronary artery disease).

Several possible reasons exist for the difference in ADT-associated cardiac risks between the Canadian database analysis and previous work. First, if an association between ADT and cardiac events exists, it is relatively small. ADT was associated with an 11–16% excess risk for cardiac events in the Keating *et al.* study[1] and a 20% excess risk in the analysis by Saigal *et al.*[3] Given this modest potential effect on cardiac events, ADT would be expected to have an even more modest effect on cardiac mortality. Indeed, several post-hoc analyses of previously completed prospective randomized controlled trials have found no convincing evidence of increased cardiovascular mortality with the use of ADT. These trials (maximum sample size 1,554) were notably under-powered to evaluate cardiovascular mortality as a clinical end point.

Second, differences in methodology might affect the detection of cardiac disease and cardiac events. All three analyses[1–3] rely on retrospective data. The first two identified patients through Medicare claims linked to the Surveillance Epidemiology and End Results (SEER) database; Alibhai *et al.*[2] used the Institute for Clinical Evaluative Sciences (ICES) databases and the Ontario Cancer Registry (OCR) to identify appropriate Canadian men. The coding of insurance claims and registry data is subject to considerable error and can vary substantially from one country and health care system to the next. In addition, while Alibhai *et al.*[2] used a `hard matching' method to identify controls in a 1:1 ratio, the previous studies included proportionally larger control groups as they analyzed all eligible men in their respective populations. Furthermore, the analyses used subtly different propensity score methods and multivariable techniques. Such differences might lead to different conclusions, particularly when the measured effect is modest.

Third, the conflicting data might reflect true differences between the populations studied. Although the analyses each include men aged at least 65–66 years with cohort mean ages in the mid-70s, American Medicare enrollees might differ from the Canadian men in the Ontario ICES database. While the Medicare analyses included men diagnosed during 1992–1999 and 1992–1996, respectively, the study by Alibhai *et al.*[2] included men diagnosed as recently as 2005. The trend toward increasing ADT use in recent years might have led to changes in the profile of the men in the treatment cohort. Finally, Alibhai and colleagues[2] uniquely included men treated with orchiectomy and with steroidal and nonsteroidal antiandrogens. These treatments might differ from GnRH agonists in their effects on cardiac morbidity.

…we must carefully weigh the benefits of ADT against its potential adverse effects

A large majority of the men with prostate cancer will die as a result of a cause other than their prostate cancer. In the SEER database (1999–2005), the overall 5-year relative survival rate for men with prostate cancer was 99.7%. Even among men with unfavorable prognosis, less than one-fifth are expected to die as a result of prostate cancer. For example, the 10-year prostate-cancer-specific mortality among such men in the RTOG 85-31 trial was 22% with deferred ADT and 15% with immediate ADT.[5] Thus, we must carefully weigh the benefits of ADT against its potential adverse effects.

As ADT is associated with an increased risk of diabetes and possibly an increased risk of cardiovascular morbidity, practical steps toward minimizing the adverse impact of this therapy are needed. No evidence-based guidelines exist specifically for the prevention of diabetes and coronary heart disease associated with ADT for prostate cancer. Nonetheless, long-term

prospective studies in the general population have compellingly shown that individuals with fewer risk factors for cardiovascular disease have a lower incidence of heart disease and stroke. In the absence of ADT-specific data, we recommend the risk-adapted use of accepted guidelines from the American Diabetes Association (ADA),[6] the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III),[7] and the American Heart Association (AHA).[8]

Smoking cessation and appropriate manage ment of hypertension are essential to control the risk of cardiovascular events in patients who receive ADT. Lifestyle can be optimized via weight control, regular physical activity, and reduced intake of saturated fat and cholesterol. Low-dose aspirin is appropriate for men with a 10-year risk of coronary heart disease of at least 10%, although its benefits must be weighed against an increased risk of major bleeds. Statins are a first-line treatment for hyperlipidemia when lifestyle interventions do not successfully bring LDL cholesterol to target levels.

ADT has been shown to reduce insulin sensitivity in prospective studies.[9] The retrospective analyses by Keating *et al.*[1] and Alibhai *et al.*[2] have each shown that ADT is associated with an increased risk of incident diabetes. We believe that men receiving ADT should, therefore, be considered at high risk of developing diabetes, and should be tested annually for this disease while receiving ADT. A recent report recommends the use of a glycosylated hemoglobin (HbA_{1c}) level ≥6.5% for the diagnosis of diabetes.[10] Individuals with an HbA_{1c} level between 6.0% and 6.5% are considered to be at highest risk for progression to diabetes, and should be counseled to pursue 5–10% weight loss and at least 150 min per week of moderate physical activity.

Diabetes and cardiovascular disease cause substantial morbidity and mortality among prostate cancer survivors. ADT for the treatment of prostate cancer increases the risk of incident diabetes and may increase the burden of cardiovascular disease. Maintaining optimum health among men treated with ADT requires careful consideration of the metabolic consequences of therapy. We argue for a proactive approach to the management of risk factors for diabetes and cardiovascular disease in these patients.

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