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Androgen Deprivation Therapy and Risk for Diabetes and Cardiovascular Disease in Prostate Cancer Survivors

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Abstract

Gonadotropin-releasing hormone (GnRH) agonists are the mainstay of treatment for recurrent and metastatic prostate cancer. GnRH agonists are also an important part of therapy for many men with localized or locally advanced prostate cancer. Although GnRH agonists improve survival in certain settings, they involve adverse effects including vasomotor flushing, obesity, and osteoporosis. This article describes the evidence that GnRH agonists increase risk for diabetes and cardiovascular disease and reviews the potential mechanisms for treatment-related morbidity.

Introduction

Androgen deprivation therapy (ADT), either by bilateral orchiectomy or administration of a gonadotropin-releasing hormone (GnRH) agonist, is the cornerstone of treatment for metastatic prostate cancer [1•]. GnRH agonists are also routinely administered to many men with locally advanced or recurrent disease [2]. GnRH agonist use has steadily increased in the past decade, with about one third of the estimated 2 million prostate cancer survivors in the United States currently receiving treatment with a GnRH agonist [3,4].

ADT involves adverse effects including vasomotor flushing, gynecomastia, obesity, and osteoporosis [1•]. In addition, GnRH agonists have recently been associated with greater risk for incident diabetes and cardiovascular disease [5••]. Several mechanisms may contribute to greater risk for treatment-related diabetes and cardiovascular disease including obesity insulin resistance, and increased serum cholesterol and triglycerides.

This article reviews the evidence that GnRH agonists increase risk for diabetes and cardiovascular disease, the potential mechanisms for treatment-related morbidity, and emerging strategies to prevent treatment-related diabetes and cardiovascular disease.

Diabetes Mellitus and Cardiovascular Disease After GnRH Agonist Treatment

A landmark study assessed the relationships between ADT and risk of diabetes mellitus and cardiovascular disease using the linked Surveillance, Epidemiology, and End Results (SEER) and Medicare database [5••]. The study included the records of 73,196 men diagnosed with local or local–regional prostate cancer from 1992 through 1999. The primary outcomes were incident diabetes mellitus, incident cardiovascular disease, and admission for myocardial infarction. Cox proportional hazards models with time-varying treatment

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variables and time-varying covariates assessed the relationship between GnRH agonist or orchiectomy and primary study outcomes. About one third of the men received a GnRH agonist. Table 1 summarizes the unadjusted rates of incident diabetes, coronary heart disease, and myocardial infarction. Rates for each of these outcomes were higher for men receiving a GnRH agonist than for untreated men. After controlling for other variables, current use of a GnRH agonist was associated with a significantly increased risk of incident diabetes (adjusted HR = 1.42; $P < 0.001$), coronary heart disease (adjusted HR = 1.16; $P < 0.001$), and admission for myocardial infarction (adjusted HR = 1.11; $P = 0.03$) compared with men receiving no ADT. Similar results were obtained using propensity score methods to match treated patients with similar untreated patients, suggesting that potential differences in baseline characteristics between the groups are unlikely to explain the observed associations.

A subsequent study using the SEER–Medicare database reached similar conclusions [6]. The study evaluated 22,816 men diagnosed with prostate cancer between 1992 and 1996. All subjects were identified after exclusion criteria were applied. Multivariate models assessed the risk of incident cardiovascular morbidity, as defined using Medicare claims. Men who received ADT for at least 1 year were found to have a 20% higher risk of cardiovascular morbidity compared with similar men who did not receive ADT. Consistent with observations by Keating et al. [5••], greater risk for cardiovascular morbidity was apparent in men with short- and long-term exposure to ADT.

Do GnRH agonists increase cardiovascular mortality?

It is unclear whether the observed treatment-related increases in incident cardiovascular disease are accompanied by higher rates of cardiovascular mortality. In analyses of the Cancer of the Prostate Strategic Urologic Research Endeavor (CAPSURE) database, neoadjuvant/adjuvant ADT appeared to be associated with higher rates of cardiovascular death [7]. The analyses included a total of 4890 men (1015 received ADT) and 131 fatal cardiovascular events. Greater risk of cardiovascular death was observed only in the subset of men who underwent radical prostatectomy. A pooled analysis of three small randomized controlled trials of radiation therapy with or without ADT for intermediate and high-risk prostate cancer reported that ADT was associated with shorter time to fatal myocardial infarction [8]. Notably, the analyses included only 51 primary events and the association was observed only in a subset of older men.

In contrast, analyses of a large, randomized, controlled trial of radiation therapy with or without long-term ADT for locally advanced prostate cancer (Radiation Therapy Oncology Group Protocol [RTOG] 85–31) found no association between ADT and cardiovascular mortality (unpublished data). There were a total of 574 deaths; 117 were categorized as cardiovascular deaths. The lack of an association between ADT and cardiovascular mortality in these analyses appeared robust based on similar results when censoring subjects at the time of salvage GnRH agonist therapy, when applying alternative definitions of cardiovascular mortality, and in analyses restricted to subsets of men at high risk for cardiovascular mortality.

Longer duration of GnRH agonist therapy was not associated with greater risk for cardiovascular mortality in recent analyses of RTOG 92–02, a randomized trial of 1554 men treated with short-term versus long-term adjuvant goserelin and radiation therapy for locally advanced prostate cancer [9]. Cox regression analyses were performed to evaluate the relationship between treatment arm and cardiovascular mortality. Covariates included age, prevalent cardiovascular disease, hypertension, diabetes, race, prostate-specific antigen level, Gleason score, and stage. There were 185 cardiovascular-related deaths. There was no increase in cardiovascular mortality for men receiving longer duration of goserelin

treatment. In multivariate analyses, cardiovascular mortality was significantly associated with traditional cardiovascular disease risk factors, such as age and prevalent cardiovascular disease and diabetes mellitus, but not duration of goserelin treatment.

What are the mechanisms for increased risk of diabetes and cardiovascular disease during GnRH agonist therapy?

GnRH agonists decrease serum concentrations of testosterone by more than 95% and estrogen by about 80% [10,11]. The effects of GnRH agonists on gonadal steroid production are reversible in most men. The severity of gonadal steroid deficiency distinguishes GnRH agonist treatment from age-related andropause.

Androgens are important determinants of body composition in men. Serum testosterone concentrations correlate positively with lean mass and negatively with fat mass in normal men [12]. GnRH agonists significantly decrease lean body mass and increase fat mass in men with prostate cancer [13–17]. In two prospective studies of men with nonmetastatic prostate cancer, treatment with a GnRH agonist decreased lean body mass by 2.7%–3.8% and increased fat mass by 9.4%–11.0% from baseline to 1 year (Table 2) [15,17]. Changes in body composition appear primarily as an early adverse effect of GnRH agonist treatment, with most of the treatment-related change in fat and lean body mass apparent within the first year of therapy [18]. Most of the treatment-related increase in fat mass is subcutaneous rather than visceral fat [17].

Adipocytokines may connect changes in body composition with metabolic alterations during GnRH agonist treatment for prostate cancer. In murine models of obesity, circulating levels of adiponectin are increased and resistin levels are decreased. Low adiponectin levels and elevated resistin levels have been implicated in insulin resistance in obese mice. In humans, plasma adiponectin levels are lower in obese individuals and most insulin-resistant states including type 2 diabetes mellitus. The role of resistin in obesity and insulin resistance in humans is controversial.

GnRH agonists significantly increase adiponectin levels in young healthy men [19]. GnRH agonists also significantly increase adiponectin levels in older men with prostate cancer [20,21•]. The relationship between adiponectin and cardiovascular disease risk is also controversial. Low adiponectin levels are associated with prevalent cardiovascular disease [22–24]. Some but not all prospective studies of healthy individuals have reported that higher adiponectin levels are associated with decreased risk of incident myocardial infarction in men and women [25–28]. In contrast, a recent prospective study reported that higher adiponectin levels are associated with greater cardiovascular mortality in men [28].

GnRH agonists also increase serum cholesterol and triglyceride levels [15,29]. In a prospective 12-month study of 40 men with nonmetastatic prostate cancer, GnRH agonist therapy increased serum total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides by 9.0%, 7.3%, 11.2%, and 26.5%, respectively [15]. Notably, most but not all of the observed long-term adverse effects on serum lipids are apparent within the first 3 months of treatment [30••].

Insulin resistance is a common metabolic abnormality that underlies type 2 diabetes mellitus and is prevalent in about one quarter of men without diabetes [31]. Importantly, insulin resistance is an independent risk factor for cardiovascular disease [32,33]. The metabolic syndrome refers to a clustering of specific cardiovascular disease risk factors whose pathophysiology appears related to insulin resistance. The National Cholesterol Education Program's Adult Treatment Panel (NCEP ATP III) and World Health Organization (WHO) define the metabolic syndrome using related criteria (Table 3) [34].

A recent cross-sectional study reported a higher prevalence of the metabolic syndrome (as defined by NCEP ATP III) in 18 men receiving a GnRH agonist than in age-matched control groups of untreated men with prostate cancer and men without prostate cancer [35•]. Men receiving GnRH agonist therapy were more likely to have increased abdominal girth, elevated triglycerides, and elevated fasting plasma glucose levels consistent with results of prospective studies of GnRH agonist treatment. In contrast to the metabolic syndrome, however, prospective studies have shown that GnRH agonists preferentially increase subcutaneous rather than visceral abdominal fat and increase rather than decrease HDL cholesterol [15]. Additionally, the metabolic syndrome is characterized by low levels of adiponectin and elevated markers of inflammation, but GnRH agonists significantly increase serum adiponectin levels and do not alter levels of C-reactive protein or other markers of inflammation [20,21•]. Thus, the observations from prospective studies suggest that GnRH agonists cause a pattern of metabolic changes that is distinct from the classically defined metabolic syndrome.

There may be practical implications of distinguishing the phenotype of men receiving GnRH agonist treatment from the classic metabolic syndrome. The clinical use of the composite definitions of the metabolic syndrome centers on its potential value as a risk factor for cardiovascular disease. The metabolic syndrome, however, is not precisely defined and may have limited independent value as a marker of cardiovascular disease risk [36,37]. Given these limitations and the dissimilar metabolic changes associated with GnRH agonist treatment, we recommend evaluation and treatment of individual risk factors for diabetes and cardiovascular disease without regard for whether an individual meets criteria for metabolic syndrome diagnosis.

Prevention of Diabetes and Cardiovascular Disease in Prostate Cancer Survivors

The association between GnRH agonists and incident diabetes and cardiovascular disease in men with prostate cancer was first described in 2006 [5••]. Not surprisingly, there is limited information about strategies to prevent treatment-related diabetes and cardiovascular disease.

In randomized, controlled trials of men and women without cancer, lifestyle intervention has been shown to reduce the risk of incident diabetes. The Diabetes Prevention Program was the only study to compare lifestyle and pharmacologic intervention with glucose-lowering medications. Lifestyle intervention was nearly twice as effective in preventing diabetes as metformin (relative risk reductions 58% and 31%, respectively) [38]. Compared with metformin, lifestyle intervention was associated with greater improvements in traditional and nontraditional cardiovascular disease risk factors including blood pressure, insulin sensitivity, HDL cholesterol, triglycerides, and C-reactive protein. In the lifestyle intervention group, these significant improvements were achieved despite modest weight loss of 6%–7% in the first year. Lifestyle interventions may be considered an ideal method for diabetes prevention in men with prostate cancer because of beneficial effects on the complete cardiovascular disease risk profile, as well as other benefits related to diet and exercise. Lifestyle intervention also appears more effective than metformin in older individuals. In the Diabetes Prevention Program, lifestyle intervention was highly effective in all subgroups including men and subjects older than age 60. In contrast, metformin was ineffective in older subjects. Compared with metformin, lifestyle intervention decreased the risk of incident diabetes by 69% (95% CI; 47%–82%) in subjects older than 60 years [38]. An ongoing, randomized controlled trial will assess whether intensive lifestyle intervention is feasible and improves insulin sensitivity during therapy in overweight and obese men

receiving a GnRH agonist for prostate cancer. Additional studies will assess the feasibility and effectiveness of other strategies, including a low carbohydrate diet.

Toremifene is a second-generation selective estrogen receptor modulator in development for the prevention of osteoporosis and other adverse effects resulting from ADT in men with prostate cancer [39]. Toremifene significantly improved serum lipid profiles in postmenopausal women [40–43]. In an interim analysis of a large, multicenter, randomized, controlled study of men receiving ADT for prostate cancer, toremifene significantly decreased total cholesterol, LDL cholesterol, and triglycerides, and increased HDL cholesterol [44]. The beneficial effects of toremifene on lipid profiles provide a strong rationale to conduct exploratory analyses of cardiovascular outcomes when the ongoing fracture prevention study is completed. The results of those analyses will help determine whether additional clinical trials are warranted to evaluate the effects of toremifene on incident coronary events in men receiving ADT for prostate cancer.

Conclusions

In men with prostate cancer, GnRH agonists are associated with greater risk of diabetes mellitus and cardiovascular disease. Treatment-related obesity and insulin resistance appear sufficient to explain the greater risk for diabetes. Several mechanisms may contribute to greater risk for cardiovascular disease including obesity, insulin resistance, and increased serum cholesterol and triglycerides. The metabolic alterations associated with GnRH agonist therapy appear distinct from the classically defined metabolic syndrome. Future research should focus on better understanding the metabolic consequences of GnRH agonist therapy and developing effective strategies to reduce treatment-related morbidity.

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Table 1

Rates of incident diabetes, coronary heart disease, and myocardial infarction in untreated and GnRH agonist–treated men with prostate cancer

	Events per 1000 person-years		
Study	**Incident diabetes**	**Incident coronary heart disease**	**Myocardial infarction**
No treatment	20.9	61.3	10.9
GnRH agonist	29.1 ($P < 0.001$)	72.4 ($P < 0.001$)	13.5 ($P < 0.001$)

GnRH—gonadotropin-releasing hormone. (*Adapted from* Keating et al. [5••].)

Table 2

Prospective studies of body composition in men treated with GnRH agonists

Study	Patients, *n*	Mean percent change from baseline to 12 months		
		Weight	Lean mass	Fat mass
Smith et al. [15]	40	+2.4% ($P = 0.005$)	−2.7% ($P < 0.001$)	+9.4% ($P < 0.001$)
Smith [17]	79	+1.8% ($P < 0.001$)	−3.8% ($P < 0.001$)	+11.0% ($P < 0.001$)

GnRH—gonadotropin-releasing hormone.

Table 3

Definitions of metabolic syndrome for men

National Cholesterol Education Program Adult Treatment Panel III
Any three or more of the following:
1 Waist circumference > 102 cm
2 Serum triglycerides ≥ 1.7 μmol/L
3 Blood pressure ≥ 130/80 mm Hg
4 High-density lipoprotein cholesterol < 1.0 μmol/L
5 Serum glucose ≥ 6.1 μmol/L (≥ 5.6 μmol/L may be applicable)
World Health Organization
Diabetes, impaired fasting glucose, impaired glucose tolerance, or insulin resistance, and at least two of the following criteria:
1 Waist-to-hip ratio > 0.90
2 Serum triglycerides ≥ 1.7 μmol/L
3 Blood pressure ≥ 140/90 mm Hg
4 Urinary albumin excretion rate > 20 μg/min or albumin-to-creatinine ratio ≥ 30 mg/g