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Treatment-related diabetes and cardiovascular disease in prostate cancer survivors

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introduction

Androgen deprivation therapy (ADT), either by bilateral orchiectomy or chronic administration of a gonadotropin-releasing hormone (GnRH) agonist, is the mainstay of treatment for metastatic prostate cancer [1]. Additionally, GnRH agonists are a standard part of the management for many men with locally advanced or recurrent disease [2]. The use of GnRH agonists has increased steadily over the past two decades [3, 4].

GnRH agonists improve survival in specific settings but have a variety of adverse effects, including vasomotor flushing, gynaecomastia, obesity and osteoporosis [1]. In addition, GnRH agonists have recently been associated with greater risk for 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 review summarizes the evidence that GnRH agonists increase risk for diabetes and cardiovascular disease, the potential mechanism(s) for treatment-related diabetes and cardiovascular disease, and emerging strategies to prevent the morbidity associated with treatment.

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 loco-regional prostate cancer from 1992 to 1999. The primary outcomes were incident diabetes mellitus, incident cardiovascular disease and admission for myocardial infarction. Cox proportional hazards models with time-varying treatment variables and time-varying covariates were used to assess the relationship between GnRH agonist or orchiectomy and primary study outcomes. About one-third of the men received treatment with a GnRH agonist. The unadjusted rates of incident diabetes, coronary heart disease and myocardial infarction were higher for men receiving a GnRH agonist than for untreated men (Table 1). After controlling for other variables, current use of a GnRH agonist was associated with a significantly increased risk of incident diabetes [adjusted hazard ratio (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 significant 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. A total of 22 816 subjects were identified after exclusion criteria were applied. In multivariate analysis, models were used to assess 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 the observations of Keating *et al.* [5], greater risk for cardiovascular morbidity was apparent in men with both short- and long-term exposure to ADT.

do GnRH agonists increase cardiovascular mortality?

Whether the observed association between GnRH agonists and incident cardiovascular disease is accompanied by greater cardiovascular mortality is unknown. Several recent studies provide some insight into the possible relationship between GnRH agonists and cardiovascular mortality in men with prostate cancer.

Table 1. Rates of incident diabetes, coronary heart disease and myocardial infarction in untreated and GnRH agonist-treated men with prostate cancer [5]

	Events per 1000 person years		
	Incident diabetes	Incident coronary heart disease	Myocardial infarction
No ADT	20.9 (reference)	61.3 (reference)	10.9 (reference)
GnRH Agonist	29.1 ($P < 0.001$)	72.4 ($P < 0.001$)	13.5 ($P < 0.001$)

P-values are for between-group comparisons.

The Radiation Therapy Oncology Group (RTOG) Protocol 8531, a large randomized controlled trial of radiation therapy with or without long-term ADT for locally advanced prostate cancer, found no association between ADT and cardiovascular mortality [7]. There was a total of 574 deaths, 117 of which 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. Recently updated results of another large RTOG study (Protocol 8610) also found no association between ADT and cardiovascular mortality [8]. In RTOG 8610, 456 men with locally advanced prostate cancer were randomly assigned to radiation therapy with or without neo-adjuvant ADT. Combined treatment with radiation therapy and ADT significantly improved disease-free survival (HR 1.52, $P = 0.009$) but not overall survival. There was a total of 348 deaths, of which 57 were classified as cardiovascular deaths. Combined modality treatment did not significantly increase cardiovascular mortality compared with radiation alone (HR 0.78, $P = 0.35$).

The European Organization for Research and Treatment of Cancer (EORTC) Trial 30891 also reported no treatment-related increase in cardiovascular mortality [9]. In that study, 985 men with newly diagnosed prostate cancer $T_{0–4}$ $N_{0–2}$ M_0 were randomly assigned to either immediate ADT ($n = 493$) or ADT at symptomatic disease progression or occurrence of serious complications ($n = 492$). Baseline characteristics were similar between the groups. At a median follow-up of 7.8 years, 541 of 985 patients had died, mostly of prostate cancer ($n = 193$) or cardiovascular disease ($n = 185$). The overall survival HR was 1.25 [95% confidence interval (CI) 1.05–1.48, non-inferiority $P > 0.1$] favouring immediate treatment, seemingly due to fewer deaths from non-prostatic cancer causes ($P = .06$). Rates of cardiovascular mortality were similar for the immediate and deferred ADT groups (17.9% vs 19.7%).

In contrast, analyses of Cancer of the Prostate Strategic Urologic Research Endeavor (CAPSURE) database suggested that neo-adjuvant/adjuvant ADT was associated with higher rates of cardiovascular death [10]. The analyses included a total of 4890 men (1015 received ADT) and 131 fatal cardiovascular events. Greater risk of cardiovascular death was observed in the subset of men who underwent radical prostatectomy but not the overall study population. A pooled analysis of three small randomized controlled trials of radiation therapy with or without ADT for intermediate- and high-risk prostate cancer also reported that ADT was associated with shorter time to fatal myocardial infarction [11]. Notably, the analyses included only 51 primary events and the association was observed only in a subset of men older than 65 years. Some have criticized the methodology and conclusions of these pooled analyses [12].

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 [13]. Cox regression analyses were performed to evaluate the relationship between treatment arms and cardiovascular mortality. Covariates included age, prevalent cardiovascular disease, hypertension, diabetes, race, prostate specific antigen (PSA) level, Gleason score and stage. There were 185 cardiovascular-related deaths. There was no increase in cardiovascular mortality for men receiving a longer duration of goserelin treatment. In multivariate analyses, traditional cardiovascular disease risk factors (including age and prevalent cardiovascular disease and diabetes mellitus) but not duration of goserelin treatment were associated with significantly greater cardiovascular mortality.

Taken together, these studies provide no compelling evidence that GnRH agonists increase cardiovascular mortality in men with localized or locally advanced prostate cancer. Notably, any increase in cardiovascular mortality associated with the GnRH agonists would probably be smaller than the observed 16–20% excess risk for incident cardiovascular morbidity observed in the SEER–Medicare studies. The retrospective studies described above included between 57 and 185 fatal cardiovascular events. Retrospective analyses of relatively small studies may be inadequate to detect a modest increase in cardiovascular mortality. Similarly, exploratory analyses of small datasets are prone to chance observations in this setting [12]. Both issues should be taken into account when considering these reports.

what are the mechanism(s) for increased risk of diabetes and cardiovascular disease during GnRH agonist therapy?

Several mechanism(s) may contribute to increases in treatment-related in risk for diabetes and cardiovascular disease including obesity, alterations in serum lipoproteins and insulin resistance.

obesity

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 [14]. GnRH agonists significantly decrease lean body mass and increase fat mass in men with prostate cancer [15–19]. In two prospective studies of men with non-metastatic prostate cancer, for example, we demonstrated that GnRH agonists decreased lean body mass by 2.7–3.8% and increase fat mass by 9.4–11.0% from baseline to 1 year ($P < 0.001$ for each comparison) [17, 19]. 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 [20]. Most of the treatment-related increase in fat mass is subcutaneous rather than visceral fat [19].

alterations in serum lipoproteins

GnRH agonists increase levels of serum cholesterol and triglycerides [17, 21]. In a prospective 12-month study of 40 men with non-metastatic prostate cancer, for example, 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 [17]. Notably, most but not all of the observed long-term adverse effects on serum lipids are apparent within the first 3 months of treatment [22].

insulin resistance

Insulin resistance is a common metabolic abnormality that underlies type 2 diabetes mellitus and is prevalent in about a quarter of non-diabetic men [23]. Importantly, insulin resistance is an independent risk factor for cardiovascular disease [24, 25]. GnRH agonists increase fasting plasma insulin levels—a marker of insulin resistance—in men with prostate cancer [16, 26]. In a 12-week prospective study of non-diabetic men, GnRH agonists significantly decreased insulin sensitivity [22]. The long-term effects of GnRH agonists on insulin sensitivity are unknown.

do GnRH agonists cause the metabolic syndrome?

The metabolic syndrome refers to a clustering of specific risk factors for cardiovascular disease whose pathophysiology appears related to insulin resistance. The National Cholesterol Education Program's Adult Treatment Panel (NCEP ATP III) and the World Health Organization (WHO) define the metabolic syndrome using different but related criteria (Table 2) [27].

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 [28]. Men receiving GnRH agonist therapy were more likely to have increased abdominal girth, elevated triglycerides and elevated fasting plasma glucose—consistent with results of prospective studies of GnRH agonist treatment.

Table 2. Definitions of metabolic syndrome for men

National Cholesterol Education Program Adult Treatment Panel III	Any three or more of the following: • Waist circumference > 102 cm • Serum triglycerides ≥ 1.7 mmol/l • Blood pressure ≥ 130/80 mm Hg • High density lipoprotein cholesterol < 1.0 mmol/l • Serum glucose ≥ 6.1 mmol/l (≥5.6 mmol/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: • Waist to hip ratio > 0.90 • Serum triglycerides ≥ 1.7 mmol/l • Blood pressure ≥ 140/90 mm Hg • Urinary albumin excretion rate > 20 μg/min or albumin-to-creatinine ratio ≥ 30 mg/g

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 [17]. 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 [29, 30]. 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 (Table 3).

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 definition(s) of the metabolic syndrome centres on its potential value as a risk factor for cardiovascular disease. The metabolic syndrome, however, is not precisely defined and has limited independent value as a marker of risk of cardiovascular disease [31, 32]. Given these limitations and the disparate metabolic changes associated with GnRH agonist treatment, I recommend evaluation and treatment of individual risk factors for diabetes and cardiovascular disease without concern for whether an individual meets diagnostic criteria for the metabolic syndrome.

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.

toremifene

Toremifene is a second-generation selective oestrogen receptor modulator in development for the prevention of osteoporosis and other adverse effects resulting from ADT in men with prostate cancer [33]. Toremifene significantly improved serum lipid profiles in post-menopausal women [34–37]. In an interim analysis of a large multicentre randomized controlled study of men receiving ADT for prostate cancer, toremifene

Table 3. Comparison metabolic changes in GnRH agonist treated men with the classic metabolic syndrome

	Classic metabolic syndrome	GnRH agonist treated men
Waist circumference	Increased	Increased
Waist-to-hip ratio	Increased	No change
Blood pressure	Increased	No change
Triglycerides	Increased	Increased
HDL cholesterol	Decreased	Increased
Fat accumulation	Visceral	Subcutaneous
Adiponectin	Decreased	Increased

significantly decreased total cholesterol, LDL cholesterol and triglycerides and increased HDL cholesterol [38]. 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.

lifestyle interventions

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 pharmacological intervention with glucose-lowering medications. Lifestyle intervention was about twice as effective as metformin in preventing diabetes [39]. Compared with metformin, lifestyle intervention was associated with greater improvements in traditional and non-traditional 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% over the first year. Lifestyle interventions may be considered an ideal method for diabetes prevention in men with prostate cancer because of the beneficial effects on the complete cardiovascular disease risk profile as well as other benefits related to diet and exercise. In addition, lifestyle intervention appears to be more effective than metformin in older individuals. Compared with metformin, lifestyle intervention decreased the risk of incident diabetes by 69% (95% CI, 47–82%) in subjects older than 60 years [39]. Our group is conducting a randomized controlled trial to assess whether intensive lifestyle intervention is feasible and improves insulin sensitivity 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.

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 of the metabolic consequences of GnRH agonist therapy and developing effective strategies to reduce treatment-related morbidity.

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disclosures

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references

1. Sharifi N, Gulley JL, Dahut WL. Androgen deprivation therapy for prostate cancer. JAMA 2005; 294: 238–244.
2. Cooperberg MR, Grossfeld GD, Lubeck DP, Carroll PR. National practice patterns and time trends in androgen ablation for localized prostate cancer. J Natl Cancer Inst 2003; 95: 981–989.
3. Barry MJ, Delorenzo MA, Walker-Corkery ES et al. The rising prevalence of androgen deprivation among older American men since the advent of prostate-specific antigen testing: a population-based cohort study. BJU Int 2006; 98: 973–978.
4. Shahinian VB, Kuo YF, Freeman JL et al. Increasing use of gonadotropin-releasing hormone agonists for the treatment of localized prostate carcinoma. Cancer 2005; 103: 1615–1624.
5. Keating NL, O'Malley AJ, Smith MR. Diabetes and cardiovascular disease during androgen deprivation for prostate cancer. J Clin Oncol 2006; 24: 4448–4456.
6. Saigal CS, Gore JL, Krupski TL et al. Androgen deprivation therapy increases cardiovascular morbidity in men with prostate cancer. Cancer 2007; 110: 1493–500.
7. Efstathiou JA, Bae K, Shipley WU. Cardiovascular mortality following androgen suppression and radiation therapy for locally advanced prostate cancer: an analysis of RTOG 85-31. J Clin Oncol 2008; In press.
8. Roach M 3rd, Bae K, Speight J et al. Short-term neoadjuvant androgen deprivation therapy and external-beam radiotherapy for locally advanced prostate cancer: long-term results of RTOG 8610. J Clin Oncol 2008; 26: 585–591.
9. Studer UE, Whelan P, Albrecht W et al. Immediate or deferred androgen deprivation for patients with prostate cancer not suitable for local treatment with curative intent: European Organisation for Research and Treatment of Cancer (EORTC) Trial 30891. J Clin Oncol 2006; 24: 1868–1876.
10. Tsai HK, D'Amico AV, Sadetsky N et al. Androgen deprivation therapy for localized prostate cancer and the risk of cardiovascular mortality. J Natl Cancer Inst 2007; 99: 1516–1524.
11. D'Amico AV, Denham JW, Crook J et al. Influence of androgen suppression therapy for prostate cancer on the frequency and timing of fatal myocardial infarctions. J Clin Oncol 2007; 25: 2420–2425.
12. Roach M 3rd. Regarding the influence of adjuvant suppression therapy for prostate cancer on the frequency and timing of fatal myocardial infarction: how real is the risk? J Clin Oncol 2007; 25: 5325–5326.
13. Efstathiou JA, Bae K, Shipley WU et al. Cardiovascular mortality and duration of androgen deprivation therapy for locally advanced prostate cancer: analysis of RTOG 92-02. Eur Urol 2008; In press.
14. Vermeulen A, Goemaere S, Kaufman JM. Testosterone, body composition and aging. J Endocrinol Invest 1999; 22: 110–116.
15. Tayek JA, Heber D, Byerley LO et al. Nutritional and metabolic effects of gonadotropin-releasing hormone agonist treatment for prostate cancer. Metabolism 1990; 39: 1314–1319.
16. Smith JC, Bennett S, Evans LM et al. The effects of induced hypogonadism on arterial stiffness, body composition, and metabolic parameters in males with prostate cancer. J Clin Endocrinol Metab 2001; 86: 4261–4267.
17. Smith MR, Finkelstein JS, McGovern FJ et al. Changes in body composition during androgen deprivation therapy for prostate cancer. J Clin Endocrinol Metab 2002; 87: 599–603.
18. Berruti A, Dogliotti L, Terrone C et al. Changes in bone mineral density, lean body mass and fat content as measured by dual energy x-ray absorptiometry in patients with prostate cancer without apparent bone metastases given androgen deprivation therapy. J Urol 2002; 167: 2361–2367.

19. Smith M. Changes in fat and lean body mass during androgen deprivation therapy for prostate cancer. Urology 2004; 63: 742–745.
20. Lee H, McGovern K, Finkelstein JS, Smith MR. Changes in bone mineral density and body composition during initial and long-term gonadotropin-releasing hormone agonist treatment for prostate carcinoma. Cancer 2005; 104: 1633–1637.
21. Eri LM, Urdal P, Bechensteen AG. Effects of the luteinizing hormone-releasing hormone agonist leuprolide on lipoproteins, fibrinogen and plasminogen activator inhibitor in patients with benign prostatic hyperplasia. J Urol 1995; 154: 100–104.
22. Smith MR, Lee H, Nathan DM. Insulin sensitivity during combined androgen blockade for prostate cancer. J Clin Endocrinol Metab 2006; 91: 1305–1308.
23. Diagnosis and classification of diabetes mellitus. Diabetes Care 2008; 31 (Suppl 1): S55–S60.
24. Despres JP, Lamarche B, Mauriege P et al. Hyperinsulinemia as an independent risk factor for ischemic heart disease. N Engl J Med 1996; 334: 952–957.
25. Pyorala M, Miettinen H, Laakso M, Pyorala K. Hyperinsulinemia predicts coronary heart disease risk in healthy middle-aged men: the 22-year follow-up results of the Helsinki Policemen Study. Circulation 1998; 98: 398–404.
26. Dockery F, Bulpitt CJ, Agarwal S et al. Testosterone suppression in men with prostate cancer leads to an increase in arterial stiffness and hyperinsulinaemia. Clin Sci (Lond) 2003; 104: 195–201.
27. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. Circulation 2002; 106: 3143–3421.
28. Braga-Basaria M, Dobs AS, Muller DC et al. Metabolic syndrome in men with prostate cancer undergoing long-term androgen-deprivation therapy. J Clin Oncol 2006; 24: 3979–3983.
29. Smith MR, Lee H, Fallon MA, Nathan DM. Adipocytokines, obesity, and insulin resistance during combined androgen blockade for prostate cancer. Urology 2008; In press.
30. Smith MR, Lee H, McGovern FJ et al. Metabolic changes during gonadotropin releasing hormone (GnRH) agonist therapy for prostate cancer:differences from the classic metabolic syndrome. Cancer 2008; In press.
31. Kahn R, Buse J, Ferrannini E, Stern M. The metabolic syndrome: time for a critical appraisal: joint statement from the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 2005; 28: 2289–2304.
32. Ferrannini E. Metabolic syndrome: a solution in search of a problem. J Clin Endocrinol Metab 2007; 92: 396–398.
33. Smith MR. Selective estrogen receptor modulators to prevent treatment-related osteoporosis. Rev Urol 2005; 7 (Suppl 3): S30–S35.
34. Erkkola R, Mattila L, Powles T et al. Bone mineral density and lipid changes during 5 years of follow-up in a study of prevention of breast cancer with toremifene in healthy, high-risk pre- and post-menopausal women. Breast Cancer Res Treat 2005; 93: 277–287.
35. Joensuu H, Holli K, Oksanen H, Valavaara R. Serum lipid levels during and after adjuvant toremifene or tamoxifen therapy for breast cancer. Breast Cancer Res Treat 2000; 63: 225–234.
36. Saarto T, Blomqvist C, Ehnholm C, Taskinen MR, Elomaa I. Antiatherogenic effects of adjuvant antiestrogens: a randomized trial comparing the effects of tamoxifen and toremifene on plasma lipid levels in postmenopausal women with node-positive breast cancer. J Clin Oncol 1996; 14: 429–433.
37. Kusama M, Miyauchi K, Aoyama H et al. Effects of toremifene (TOR) and tamoxifen (TAM) on serum lipids in postmenopausal patients with breast cancer. Breast Cancer Res Treat 2004; 88: 1–8.
38. Smith M, Malkowicz SB, Chu F et al. Toremifene improves lipid profiles in men receiving androgen deprivation therapy for prostate cancer-interim analysis of a multicenter phase III study. J Clin Oncol 2008; In press.
39. Knowler WC, Barrett-Connor E, Fowler SE et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med 2002; 346: 393–403.