Metabolic Complications of Androgen Deprivation Therapy for Prostate Cancer

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Abstract

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.

Keywords

prostatic neoplasms; gonadotropin-releasing hormone agonists; cardiovascular diseases; diabetes mellitus; obesity

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 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% ($\pm0.8\%$, p = 0.005), percentage fat body mass increased by 9.4% ($\pm1.7\%$, p <0.001) and percentage lean body mass decreased by 2.7% ($\pm0.5\%$, p <0.001). Similarly a larger study of 79 men with nonmetastatic prostate cancer also showed significant weight gain (1.8% $\pm0.5\%$, p <0.001) during 1 year of ADT.[17] Percentage fat mass increased (11.0% $\pm1.7\%$) and percentage lean mass decreased (3.8% $\pm0.6\%$). 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.

LIPID ALTERATIONS

GnRH agonists cause several characteristic changes in serum lipids. Multiple studies have demonstrated increases primarily in total cholesterol, triglycerides and HDL.[15,24,25] An early study of 26 patients receiving 24 weeks of the GnRH agonist leuprolide acetate for benign prostatic hyperplasia demonstrated increases in total cholesterol (10.6%, p = 0.003), HDL (8.2%, p = 0.052) and triglycerides (26.9%, p = 0.050). LDL did not change significantly.[25] One year of GnRH agonist therapy in a group of 40 men with prostate cancer was later found to cause significant increases in cholesterol (9.0%), HDL (11.3%), LDL (7.3%) and triglycerides (26.5%).[15] In another study men experienced significant increases in total cholesterol and HDL during the first 3 months of GnRH agonist treatment.[24]

Awareness of the potential for these changes can prompt appropriate management and facilitate CV risk reduction. Large cohort analyses show a strong, continuous, graded relationship between serum cholesterol and cardiovascular mortality independent of other coronary risk factors such as blood pressure and smoking status.[26,27]

The NCEP ATP-III provides guidelines for the evaluation and treatment of high cholesterol in the general population.[28] These guidelines outline the assessment of CHD risk in each patient, the assignment of an appropriate LDL target for each patient and appropriate interventions to achieve the LDL target. In addition to diet and lifestyle interventions, statin drugs are the mainstays of pharmacological management and have been shown in a large meta-analysis to reduce all cause mortality by approximately 16%.[29]

INSULIN RESISTANCE

Insulin resistance is a metabolic abnormality that accompanies diabetes, prediabetes and obesity. It is an independent risk factor for cardiovascular disease and is present in about a fourth of adults in the general population.[30,31] Impaired insulin sensitivity in response to GnRH

agonists is an early development, and is likely relevant to the risks of diabetes, coronary artery disease, myocardial infarction and sudden death.[32] Men with prostate cancer are further burdened as GnRH agonists increase fasting insulin levels[20,24] and decrease sensitivity to insulin.[19,21]

Insulin resistance is illustrated in figure 2. While serum glucose curves during the OGTT are identical after 12 weeks of combined androgen blockade, insulin levels significantly increase from baseline.[19] In a prospective study of 22 men receiving GnRH treatment for prostate cancer, median fasting serum insulin increased progressively from 11.8 at baseline to 15.1 mU/l (p = 0.021) at 1 month and to 19.3 mU/l (p = 0.020) at 3 months.[20] In a 3-month study of 16 men initiating GnRH agonist treatment, fasting insulin levels nearly doubled from 6.89 ($\pm$4.84) to 11.34 ($\pm$8.16) mU/l.[24]

A prospective 12-week study of 25 men receiving combined androgen blockade with a GnRH agonist and bicalutamide demonstrated a 13% decrease (p = 0.02) in the insulin sensitivity index (calculated from results of the oral glucose tolerance test[33]).[21] Insulin sensitivity by homeostatic model assessment decreased similarly. Fasting plasma insulin levels increased by 26% (p = 0.04) and mean glycosylated hemoglobin also increased significantly (p<0.001).

The ADA recommends that patients with impaired glucose tolerance or impaired fasting glucose (IGT or IFG, see Appendix) should be given counseling on weight loss of 5% to 10% of body weight and on increasing physical activity to at least 150 minutes per week of moderate activity such as walking.[34]

THE METABOLIC SYNDROME

The metabolic syndrome is a cluster of CV risk factors that seem to center on insulin resistance. [35,36] Diagnosis of the syndrome requires some combination of low HDL, increased waist circumference, increased triglycerides, increased fasting glucose and hypertension. Consistent with the observations from prospective studies that ADT increases abdominal fat area and triglycerides, and decreases insulin sensitivity, cross-sectional studies have shown that men receiving ADT are more likely to meet the diagnostic criteria for the syndrome.[18,37]

Although the metabolic alterations of ADT share some of the features of the classically defined metabolic syndrome, there are important differences (table 1). Distinct from the metabolic syndrome, ADT associated changes feature an increased HDL. In addition, ADT has been shown in 2 prospective studies to cause increases in subcutaneous rather than visceral abdominal fat.[15,18] Finally, the metabolic syndrome is associated with low levels of adiponectin[38] and an increased C-reactive protein[39] while GnRH agonists are associated with increased adiponectin and unchanged C-reactive protein levels.[18,19]

The concept of the metabolic syndrome in any population has recently been called into question as it does not dependably add to the predictive value of traditional risk factors for diabetes or cardiovascular disease.[35,36] In a recent review of 2 large prospective studies that included a combined total of 6,955 patients, the diagnosis of metabolic syndrome was no better at predicting incident diabetes than the presence of increased FPG (110 mg/dl or greater).[40] The ADA has recommended the evaluation and treatment of all cardiovascular disease risk factors regardless of whether a patient meets the diagnostic criteria for the metabolic syndrome.[36] Despite some overlap the metabolic changes that accompany GnRH agonist therapy are distinct from the classically defined metabolic syndrome. These differences and the doubtful prognostic value of the syndrome itself contraindicate its use in the clinical care of men receiving ADT.

DIABETES

Insulin sensitivity decreases as BMI increases.[41] Obesity and insulin resistance are strongly associated with type 2 diabetes.[42] Prompted by their prospective observation that GnRH agonists increase fat mass and decrease insulin sensitivity, Keating et al conducted a large population based study to evaluate the potential relationship between ADT and the new diagnosis of diabetes.[32] They used SEER and Medicare databases to study the records of 73,196 men 66 years old or older who had been diagnosed with locoregional prostate cancer between 1992 and 1999 and observed through 2001. Among the third of those men who received a GnRH agonist during the followup period, the adjusted hazard ratio was higher for incident diabetes (HR 1.44, p <0.001). The 7% who underwent bilateral orchiectomy were also significantly more likely to have diabetes (AHR 1.34). Similarly analysis of a Canadian database including approximately 20,000 men 66 years old or older treated for prostate cancer found that diabetes was 16% more likely to develop in these men than in matched controls in a preliminary report.[43] Although the ADA does not specifically list hypogonadism as a risk factor for diabetes, we recommend treating all men receiving ADT as high risk individuals based on recent data about the effect of ADT on insulin sensitivity[19,21] and its association with diabetes (see Appendix for adapted ADA recommendations).[32,34,43]

CARDIOVASCULAR MORBIDITY AND MORTALITY

Given that ADT associated obesity, insulin resistance and increased triglycerides suggest a greater risk of cardiovascular disease, Keating et al also evaluated the relationship between ADT and new cardiovascular disease.[32] The men who received a GnRH agonist had a higher incidence of CHD (HR 1.16, p <0.001), myocardial infarction (HR 1.11, p = 0.03) and ventricular arrhythmia/SCD (HR 1.16, p = 0.004; note: sudden cardiac death does not necessarily result in patient death). Notably the excess risk of new diabetes (HR 1.44) was approximately 3 times that of new cardiovascular disease (HR 1.16, fig. 3). Risks for coronary heart disease, myocardial infarction and sudden cardiac death were not increased in the men who underwent bilateral orchiectomy.

Some but not all studies have confirmed an association between ADT and greater risk of cardiovascular disease (tables 2 and 3). Retrospective population based analysis of almost 23,000 men with prostate cancer similarly showed that ADT caused a 20% increase in the risk of serious cardiovascular morbidity at 1 year.[44] In contrast, a preliminary report of analyses of a Canadian database of approximately 20,000 men 66 years old or older treated for prostate cancer showed no increase in the risk of acute myocardial infarction.[43] The absence of an association between ADT and risk of cardiovascular events in this study may reflect inadequate power to detect a numerically modest effect, different methods of ascertainment of new cardiovascular disease or differences in the population studied.

The possible association between GnRH agonists and cardiovascular mortality has been the subject of several analyses (tables 2 and 3). Although ADT is significantly associated with incident diabetes and cardiovascular morbidity, these trials do not consistently describe a significant relationship between ADT and cardiovascular death.

Three large RTOG trials have shown comparable cardiovascular mortality regardless of ADT assignment. 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.[45] A total of 117 cardiovascular related deaths occurred during the 8.1-year followup.[46] Cardiovascular mortality was 8.4% with indefinite ADT and 11.4% when ADT was started only on evidence of recurrence, a nonsignificant difference.

In RTOG 86-10, 456 men with locally advanced prostate cancer were randomized to radiation alone or to radiation with 4 months of neoadjuvant combined androgen blockade.[47] Of the 348 deaths during 10 years of followup, 57 were classified as cardiovascular deaths. There was no significant difference in cardiovascular mortality between the radiation alone group (11%) and the combined therapy group (14%, p = 0.32 for the comparison).

In RTOG 92-02, 1,554 men with locally advanced prostate cancer were randomized to radiation with 4 or 28 months of ADT with a GnRH agonist.[48] There were 185 cardiovascular related deaths during the 8.1-year followup. The 5-year cardiovascular mortality was 5.9% with long duration ADT and 4.8% with short duration ADT (HR 1.09, p = 0.58), a nonsignificant difference. The absence of a significant difference between treatment groups suggested no increase in cardiovascular mortality risk with increasing duration of GnRH agonist treatment. Well described cardiac risk factors such as age, diabetes and personal history of coronary artery disease maintained their predictive value.

EORTC trial 30891 showed no difference in cardiovascular mortality based on timing of ADT. [49] This trial enrolled 985 men with prostate cancer not suitable for local treatment and randomized them to ADT either immediately, or deferred until symptomatic progression or serious complications. The median time from randomization to the start of treatment in the deferred group was 7 years. There were 185 deaths due to cardiovascular disease and 193 due to prostate cancer during the 7.8 years of followup. Of those deaths 88 (17.9%) occurred in the immediate ADT group and 97 (19.7%) occurred in the deferred ADT group, a nonsignificant difference. The overall survival hazard ratio was 1.25 (95% CI 1.05–1.48) favoring immediate treatment.

The CaPSURE database has been the only source to show a statistically significant ADT attributable risk of cardiovascular death.[50] For the 3,262 men in the database who were treated with radical prostatectomy, older age (continuous variable, AHR 1.07; p = 0.003) and neoadjuvant ADT (AHR 2.6, p = 0.002) were the only factors independently associated with death from cardiovascular causes. In contrast, baseline heart disease and diabetes were not. ADT caused a trend toward increased cardiovascular death at 5 years in men of all ages. This finding was statistically significant in men 65 years old or older, in whom the incidence of cardiovascular death was 5.5% with ADT and 2.0% without (61 total events, p = 0.002). Similar differences were observed in patients treated with radiation but were not statistically significant.

Combined analysis of 3 randomized trials of men treated with radiation for intermediate or high risk prostate cancer suggested that men 65 years old or older treated with 6 months of ADT experienced earlier onset of fatal myocardial infarction than those who did not receive ADT.[51] The statistical methods used to reach this conclusion have been questioned, particularly with reference to the small number of events (18 in the ADT group and 16 in the control group). [52]

There is no convincing evidence that ADT is associated with greater cardiovascular mortality. This absence of a persuasive association between ADT and cardiovascular mortality is consistent with the modest relative risk for new cardiovascular disease in men receiving GnRH agonists for prostate cancer. For example, in a large population based study Keating et al observed an excess risk of hospital admission for MI of 11% (fig. 3).[32] Assuming this is a reliable estimate of the risk of MI, the excess risk of cardiovascular mortality would be expected to be well below 11%. Retrospective analysis of relatively small studies would generally be inadequate to detect such a small increase in cardiovascular mortality. Exploratory analysis of smaller studies with low numbers of events could be subject to chance observations.[52]

CONCLUSIONS AND RECOMMENDATIONS

Diabetes and cardiovascular disease are among the leading causes of noncancer death in patients with cancer, accounting for 35% of noncancer deaths in 1 analysis.[53] GnRH agonists, widely used for the treatment of prostate cancer, are associated with several metabolic changes (obesity, insulin resistance and lipid alterations), and an increased risk of diabetes and cardiovascular events. Therefore, it is important to understand and manage those metabolic changes. In the absence of high level evidence specific to men with prostate cancer, we recommend following well established guidelines on the screening and management of these changes in the general population. ADA screening recommendations for prediabetes and diabetes are described in the Appendix.

Optimal management strategies for the GnRH associated changes in body composition and insulin resistance have not yet been defined. According to the ATP-III the 2 general goals when managing insulin resistance are to treat the underlying cause when possible and to treat cardiovascular risk factors individually if they persist despite lifestyle modifications.[54] The ADA specifically recommends counseling patients with IGT or IFG to strive for 5% to 10% weight loss and at least 150 minutes per week of moderate exercise.

In men and women without cancer lifestyle intervention targeting weight loss and increased physical activity was shown to be approximately twice as effective as metformin at reducing the risk of incident diabetes.[55] Randomized study of intensive lifestyle intervention to improve insulin sensitivity and markers of cardiovascular disease in men receiving GnRH agonists is ongoing. Resistance exercise training during GnRH agonist treatment does not prevent weight gain but has been shown to decrease treatment related fatigue, and improve quality of life and muscular fitness.

Appropriately aggressive management of hyper-lipidemia has been effective in the general management of cardiovascular disease and should likely be a component of medical care for men receiving ADT for prostate cancer. The NCEP ATP-III guidelines describe the assignment of a risk adjusted LDL target and first line use of statins when lifestyle interventions are inadequate to reach that target. Toremifene has shown promise for the management of GnRH agonist associated lipid changes but its effect on cardiovascular outcomes has not yet been studied.

Physicians and patients should consider the metabolic side effects, and 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. This includes screening for prediabetes/diabetes according to ADA guidelines, lifestyle modifications according to ADA guidelines and management of lipids according to NCEP ATP III guidelines. Finally, physicians and patients alike should support survivorship research to further our understanding and improve our management of these important issues.

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

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APPENDIX

Adapted ADA recommendations for the diagnosis of prediabetes and diabetes[34]

The current ADA guideline does not include hypogonadism as a risk factor for diabetes. We recommend treating all men receiving ADT as high risk individuals based on recent data about the effect of ADT on insulin sensitivity and its association with diabetes.

- Consider testing in all asymptomatic adults

- If testing is normal, repeat yearly while receiving ADT and at least every 3 years otherwise

- Appropriate tests: FPG or 2-hr OGTT (75 gm glucose load)

- FPG is the preferred test

- The use of hemoglobin A1C for the diagnosis of diabetes is not recommended

- Diagnosis of prediabetes (either of the following):
    - IFG = FPG 100–125 mg/dl
    - IGT = 2-hr plasma glucose 140–199 mg/dl (on OGTT)

- Criteria for the diagnosis of diabetes (any 1 of the following):
    - FPG 126 mg/dl or greater (fasting defined as no caloric intake for 8 or more hours)
    - Symptoms of hyperglycemia (polyuria, polydipsia, unexplained weight loss) with a casual plasma glucose of 200 mg/dl or greater
    - 2-Hr plasma glucose greater than 200 mg/dl during an OGTT (75 gm glucose)

- An OGTT may be considered in patients with IFG to better define the risk of diabetes

- In those identified with prediabetes identify and, if appropriate, treat other cardiovascular disease risk factors
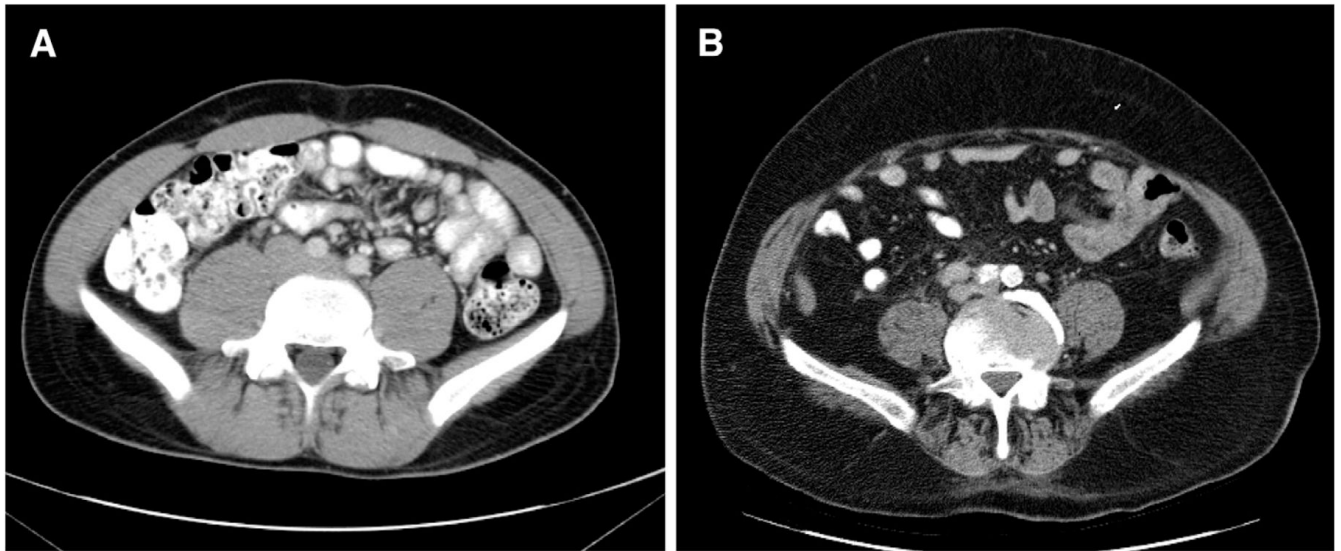
Figure 1.
GnRH agonist associated sarcopenic obesity. GnRH agonists increase abdominal cross-sectional area primarily through accumulation of subcutaneous fat. Cross-sectional images of young healthy man (*A*) and of obese man receiving long-term GnRH agonist therapy (*B*). Note relative paucity of abdominal and paraspinal musculature, and accumulation of subcutaneous fat.
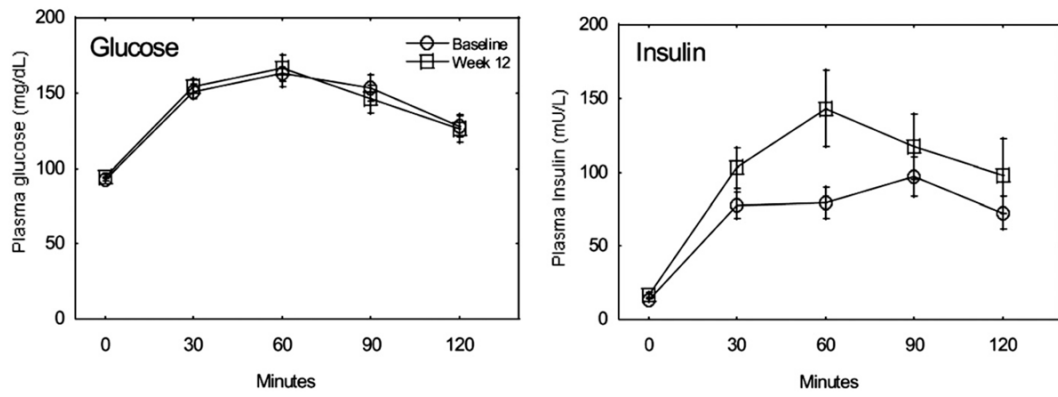
Figure 2.
Insulin sensitivity decreases during GnRH agonist therapy. Glucose and insulin levels throughout oral glucose tolerance test. Data are taken at baseline (circles) and after 12 weeks of androgen blockade (squares).[19]
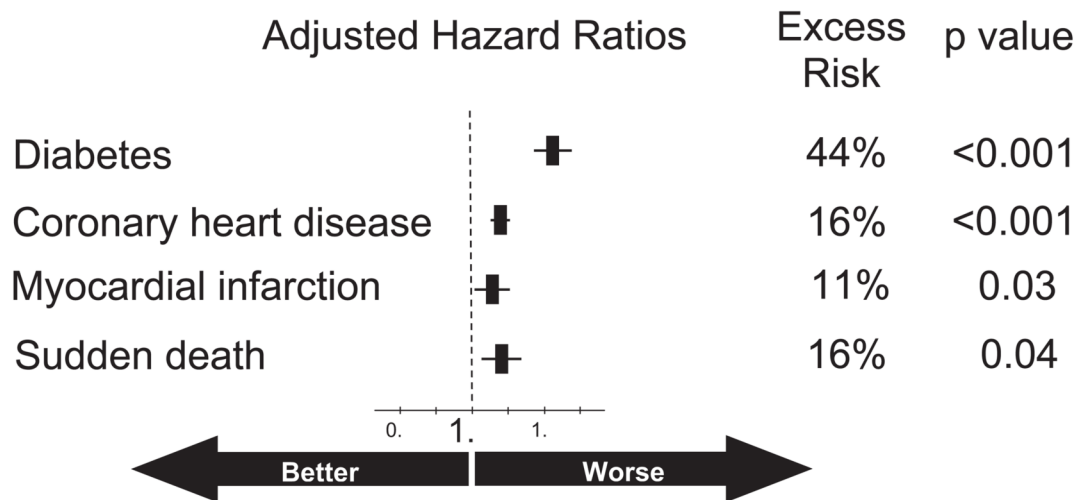
Figure 3.
GnRH agonists are associated with significant excess risk of diabetes, coronary heart disease, myocardial infarction and sudden death. Largest excess risk is for diabetes (44%).[32]

Table 1

Prospective data on the metabolic changes caused by ADT

End Points	Observations	Comment
Body composition:		
Wt gain	Gain ~2% in 12 mos[15,17,56]	Prospective lifestyle intervention to prevent wt gain is ongoing
Fat body mass	Gain 4%–8% in 3 mos,[19,20] gain ~10% in 12 mos[15,17,18]	Subcutaneous abdominal fat area increases while intra- abdominal fat remains unchanged[15,18]
Lean body mass	Lose ~3% in first 3–12 mos[15,17,18,20]	Loss of lean body mass with concurrent fat gain described as sarcopenic obesity
Serum lipids:		
Total cholesterol	Increases 7%–10% in first 3–12 mos of therapy[15,24,25]	
Triglycerides	Increases 26% in first 3–6 mos of therapy[15,25]	
HDL	Increases 8%–20% in 3–12 mos of therapy[15,24,25]	HDL decreased ~5% in 12 mos in 1 study[57]
LDL	No change in 3–6 mos[24,25]	Increase of 7% in first 3 mos in 1 study[15]
Insulin sensitivity:		
Fasting insulin	Increases 26%–65% in first 12 wks[20,21,24]	Serum glucose does not change significantly in first 3 mos[24]
Insulin sensitivity index	Decreases ~13% in 12 wks[19,21]	Calculated from OGTT

Table 2

The effects of ADT on clinical end points in population based studies

Data Source	Population	Events	Results	Comments/Conclusions
SEER/Medicare[32]	73,196 Medicare enrollees 66 yrs or older with locoregional prostate Ca, 64,721 without prevalent diabetes, 59,748 without prevalent CHD	Incident diabetes 7,055 (10.9%), incident MI 3,917 (5.4%), incident CHD 15,116 (25.3%), incident SCD 3,301 (4.5%)	AHR for incident diabetes 1.44 (p <0.001), AHR for MI 1.11 (p = 0.03), AHR for CHD 1.16 (p <0.001), AHR for SCD 1.16 (p = 0.004)	About 1/3 pts received GnRH agonists. For men treated with orchiectomy AHR for diabetes was 1.34 (p <0.001) but no excess risk of MI, CHD or SCD observed
SEER/Medicare[44]	22,816 Men 66 yrs or older diagnosed with any stage new prostate Ca	Serious CV morbidity for men who received ADT 2,653 (55%)	AHR for serious CV morbidity 1.20 (95% CI1.146–1.257)	4,810 (21%) Men received GnRH agonists, control cohort was 18,006; analysis controlled for age, race, comorbidity score, history of CHD + other factors
Canadian database[43]	Linked databases of men66 yrs or older with prostate Ca in Ontario, Canada, 19,709 treated with 6 or more mos ADT	Incident diabetes, incident MI	AHR for incident diabetes1.16 (95% CI 1.11–1.21), AHR for incident MI0.91 (95% CI 0.84–1.00)	19,709 Men treated with ADT matched to similar pts with prostate Ca not treated with ADT
CaPSURE[50]	Database of men treated with radical prostatectomy 3 ADT	Cardiovascular deaths 61	5.5% with immediate ADT, 2.0% without ADT	Trend toward increased CV mortality significant only in men older than 65 yrs (p = 0.002 for that group)

Table 3

Post hoc analyses of completed randomized controlled trials

Study	Population	Groups Compared	No. CV Deaths	CV Mortality	Comments/Conclusions
Pooled data[51]	Combination of trials for men treated for intermediate or high risk prostate Ca	6 Mos adjuvant ADT vs no ADT	34	18 CV deaths with ADT, 16 without ADT	Statistical analysis confined only to men older than 65 yrs event rate was equivalent but CV deaths sooner with ADT
RTOG 85-31[46]	Unfavorable prognosis prostate Ca (T3 tumor or nodal involvement)	RT + indefinite ADT vs RT alone	117	8.4% With ADT, 11.4% without ADT	No significant difference between treatment groups (p = 0.17)
RTOG 86-10[47]	Locally advanced prostate Ca	RT + 4 mos combined ADT vs RT alone	57	14% With ADT, 11% without ADT	No significant difference between treatment groups (p = 0.32)
RTOG 92-02[48]	Locally advanced prostate Ca	RT + ADT (28 mos) vs RT + ADT (4 mos)	185	5-Yr CV mortality, 5.9% with 28 mos ADT, 4.8% with 4 mos ADT	No significant difference between treatment groups (p = 0.58)
EORTC 30891[49]	Prostate Ca not suitable for local treatment	Immediate ADT vs ADT deferred until symptomatic	185	17.9% With immediate ADT, 19.7% with deferred ADT	No significant difference between treatment groups