Prostate Cancer Foundation
Curing Together.

SURVIVORSHIP MONOGRAPH

MAINTAINING HEALTH *during* ANDROGEN DEPRIVATION THERAPY

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The Prostate Cancer Foundation (PCF) is the world's leading philanthropic organization funding and accelerating prostate cancer research. Founded in 1993, PCF has raised over $670 million and has provided funding to more than 2,000 research programs at nearly 200 universities and university cancer centers in 19 countries. PCF advocates for greater awareness of prostate cancer and faster, more innovative investments in transformational cancer research.

Survival rates for prostate cancer have steadily increased in recent decades. For all stages of prostate cancer combined, the 5-year survival rates are now almost 100%. PCF is a force of hope for men and their families around the world who are currently facing this disease.

Men with prostate cancer are living longer, but many survive with a greater burden of treatment. More than one-third of the nearly three million prostate cancer survivors in the United States currently receive androgen deprivation therapy (ADT). ADT improves the clinical outcomes for men with prostate cancer in certain settings, but has a variety of adverse effects that may impact their long-term health. This guide presents the latest information about these potential adverse effects and describes best practices for men to maintain health during ADT.

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Foreword

In 1971 the Federal Government declared a "war on cancer". We are all familiar with the fact that by not committing the necessary resources, this war has been waged with insufficient ferocity to achieve its ultimate victory.

Today, roughly one in two men and one in three women can expect to get cancer in their lifetimes. Sadly, the American Cancer Society projected that 589,430 Americans (one every 54 seconds) died of cancer in 2015.

Despite these sobering statistics, many battles have and are being won. They have produced steady and measurable benefits. These include the fact that the five-year survival of all cancers between 2003-2009 rose to 68% compared to 49% from 1975-1977. Cancer death rates have dropped in the U.S. for each of the past 10 years. Moreover, the most spectacular improvement has occurred in the two most commonly diagnosed cancers, prostate and breast, where the five year survival of both exceeds 90% compared to survivals in 1975 of 68% for prostate and 75% for breast cancer. Relevant to this discussion is the fact that there are currently 14.5 million cancer survivors in the U.S., a number that is projected to increase to 18 million in 2022.

Throughout its history, starting with its groundbreaking Nutrition Monograph, PCF has responded to timely and important issues by publishing white papers. These publications serve a dual purpose. First, they provide an in-depth look at the state of the science of all knowledge of the field. Second, they become the basis for formulating the most important unanswered questions identified in the analysis. These unanswered questions become the subject of PCF-initiated RFAs for competitive Challenge Awards which are intended to recruit the most talented researchers to focus on answers to these questions. This monograph is therefore designed not only to inform patients and their physicians on the best current standards of care, but to act as a call to arms for the scientific community to help expand those standards with evidence-based solutions.

The title of this monograph is "Maintaining Health during Androgen Deprivation Therapy." The improved survivorship, previously noted, has made this issue timely and relevant. Despite the recent FDA approval of multiple exciting new treatments for advanced prostate cancer, long-term ADT remains–and is likely to remain–the cornerstone of treatment. Clinicians routinely care for men taking these drugs for ten, and in some cases, 20 years. We have an increasing body of knowledge that suggests that many patients who are successfully treated for their cancer are succumbing to collateral illnesses produced by their treatments. There is a desperate need to better understand this ironic paradox to prevent it from occurring and to manage it more effectively when it does.

This monograph, initiated by the PCF scientific leadership team, is edited by Dr. Mathew Smith, a recognized leader in this area, who has invited a global consortium of prominent scientists and physician-scientists to contribute to the monograph in their particular areas of expertise. We have collectively tried to identify and examine all relevant issues, most of which have only recently come to light with improved survival. We believe that many of these current issues are not being addressed in the majority of men undergoing treatment and hope this effort will focus the necessary attention to these issues and serve as a catalyst for change. We thank all the contributors for volunteering their time and very enthusiastically endorse their findings as being the best available in the field. We believe this document will help both current and future patients achieve long-term, high quality-of-life survival and further the PCF mission of ending death and suffering from prostate cancer.

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Introduction

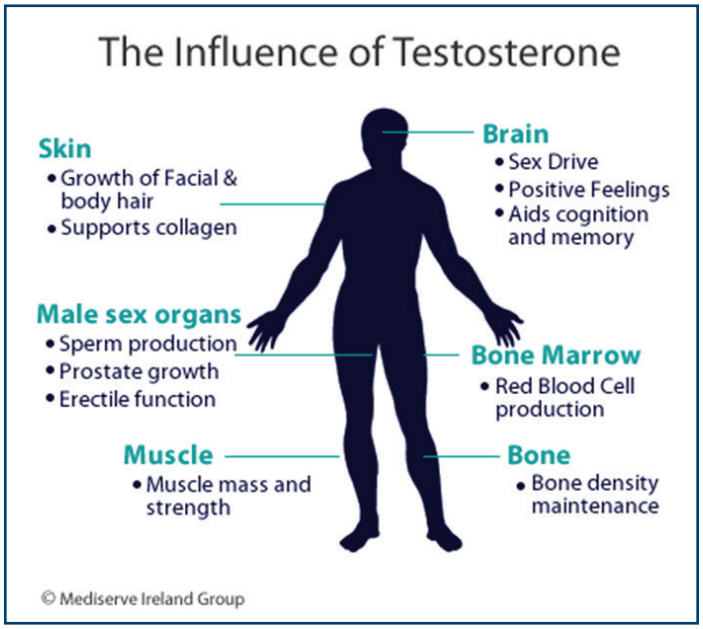
There are nearly 3 million prostate cancer survivors in the United States and millions more worldwide. In 2015, about 220,800 men will be diagnosed with prostate cancer in the United States and 27,540 are projected to die from the disease. Survival rates from prostate cancer have improved in recent decades. These improvements in survival have been attributed to earlier diagnosis, earlier treatment and more effective treatment options for men with metastatic disease.

Androgen deprivation therapy (ADT) is the cornerstone of treatment for metastatic prostate cancer and an important part of care for many men with earlier stage disease. ADT delays disease progression and increases survival in certain disease states but has a variety of potential harms including obesity, sarcopenia, osteoporosis, metabolic alterations and greater risks for clinical fractures and diabetes. For some men, the cumulative harms from ADT and risk for age-related diseases may be more important than the threat from prostate cancer. The primary focus for many survivors is to live free from prostate cancer. Survivors may also benefit from focusing on their general health in order to improve the length and quality of their lives.

This guide was developed to inform patients and clinicians about the side effects of ADT and strategies to prevent treatment-related harms. A working group of leading experts in prostate cancer, epidemiology and internal medicine were gathered from across the United States and Europe to help develop this guide. The guide provides the latest information about the potential adverse effects of ADT and describes best practices to maintain health and prevent age-related diseases during long-term treatment.

Biology of Sex Steroids

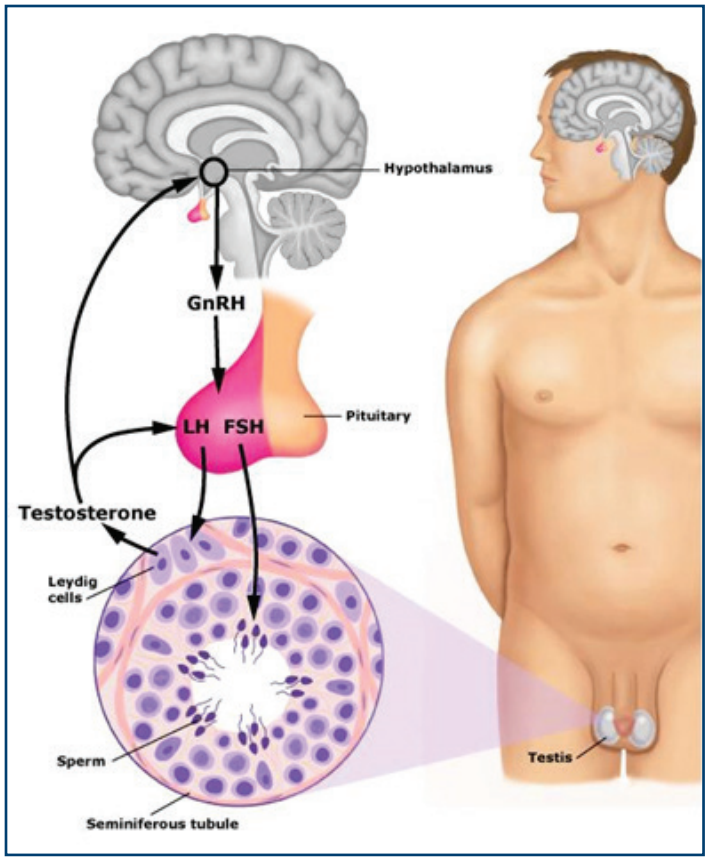
The two main classes of sex steroids are androgens or "male hormones" and estrogens or "female hormones." Androgens and estrogens are present in both men and women, though at different levels. The most important androgen and estrogen are testosterone and estradiol, respectively. In men, testosterone is produced primarily by the testes. Serum testosterone levels are maintained within normal limits by negative feedback. More than 80% of estradiol in men is derived by conversion from testosterone.



Sex steroids have important physiologic functions in normal men.[1] Androgens promote sexual function, muscle development and function and red blood cell production. Androgens also have positive effects on mood and cognition. Estrogens inhibit fat accumulation. Both androgens and estrogens have important roles in bone metabolism.

Normal serum testosterone levels for adult men are 300-1,200 ng/dL. Serum testosterone levels

decline modestly as men age. Approximately 20% of men older than 60 years of age and 50% of men older than 80 years of age have low testosterone levels (defined as at least 2 standard deviations below the mean level in young men).[2,3] The Endocrine Society recommends diagnosis of hypogonadism only in men with consistent signs and symptoms of androgen deficiency and unequivocally low serum testosterone levels.[4]

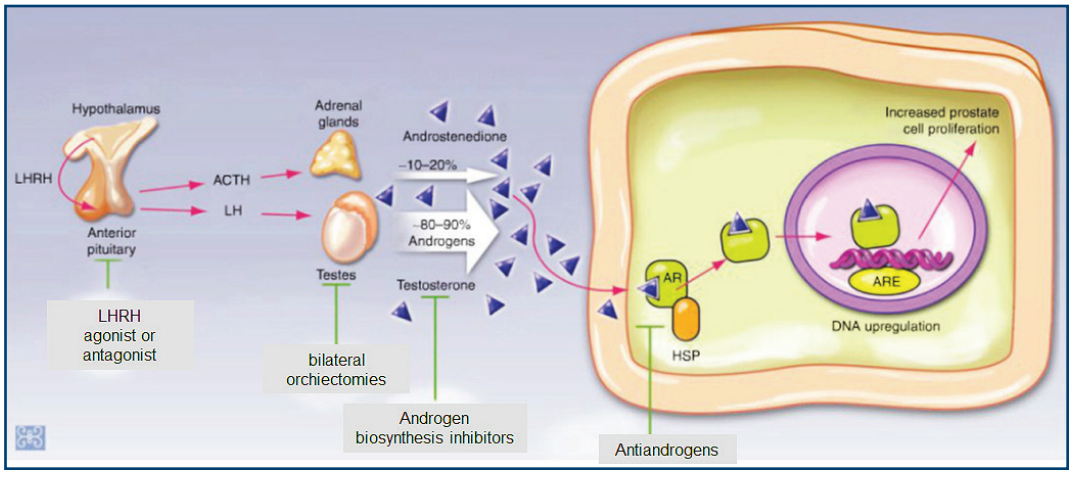


Androgen Deprivation Therapy (ADT)

Prostate cancers uniformly have androgen receptors and testosterone promotes the growth and survival of prostate cancer cells. Androgen deprivation therapy (ADT) is the mainstay of treatment for metastatic prostate cancer. ADT is also a standard part of care for many men with non-metastatic disease. ADT is achieved by either surgical removal of the testes (orchiectomies) or treatment with a gonadotropin releasing hormone (GnRH) agonist or antagonist. Most men receive ADT with medication rather than surgery because GnRH agonists and antagonists are easily administered, reversible and more acceptable to most patients.

The intended effect of ADT is severe androgen deficiency. ADT decreases serum testosterone levels to <20 ng/dL in most patients. Because estradiol in men is derived primarily by conversion from testosterone, ADT also results in severe estrogen deficiency. The severity of sex steroid deficiency distinguishes ADT from hypogonadism associated with aging or other medical conditions.

ADT improves prostate cancer outcomes in certain clinical settings. For men with metastatic prostate cancer, ADT is associated with high rates of response, decreased cancer-related symptoms and increased survival.[5] For men with high-risk early stage prostate cancer,



the addition of long-term ADT (28-36 months) to external beam radiation therapy improves disease-specific and overall survival.[6,7] The addition of short-term ADT (4-6 months) to radiation therapy also improves clinical outcomes for men receiving radiation therapy for intermediate-risk early-stage prostate cancer. Lifelong adjuvant ADT improves survival in men with node-positive disease after radical prostatectomy.[8] Notably, ADT is often used in other settings where the effects on disease-specific and overall survival are unknown. ADT is commonly administered to men with rising prostate-specific antigen (PSA) levels after surgery or radiation therapy for early-stage prostate cancer, for example, though the benefits and harms of early ADT for men with "PSA-only" prostate cancer recurrences have not been adequately characterized.[9]

Adverse effects of ADT have important implications to the long-term health of prostate cancer survivors. About one-third of the nearly 3 million prostate cancer survivors in the United States currently receive ADT.[10,11] Many of these men are medically vulnerable because of older age and co-morbid medical conditions. ADT results in vasomotor flushing, decreased libido, anemia and fatigue. ADT also increases the risk for additional medical problems including osteoporosis, obesity, sarcopenia and diabetes. This monograph summarizes the adverse effects of ADT and describes best practices to maintain health during long-term treatment.

Prevalence and Trends in Use of Androgen Deprivation Therapy (ADT)

Many men with prostate cancer receive ADT sometime during their clinical course. Frequency of ADT use varies by a patient's clinical and demographic features, geography and time.

Rates of ADT use in the United States are among the highest in the world. Between 2000-2005, 45% of United States men aged 65 and older received ADT during the first year post-diagnosis.[12] One-third of these men initiated ADT as adjuvant therapy with radiation and another third as primary ADT. Nearly all men received ADT with a GnRH agonist. ADT use was substantially higher in men with locally advanced cancer, with 35% using radiation plus ADT and 36% receiving ADT alone within 6 months of diagnosis.[13] A similar proportion of men of all ages with localized prostate cancer received ADT as primary therapy,[14] although use varied by age: <5% for men age 65 and younger and 42% for men age 75 and older. Primary ADT was more common for men with existing medical conditions and varied by risk group, race/ethnicity and by practice.

Rates of ADT use increased markedly in the United States during the 1990s. While rates of surgery and radiation therapy in the US have remained relatively stable during the last three decades, the proportion of men aged 65 and older treated with ADT within 12 months of diagnosis increased from 23% in 1991 to 43% in 1999.10 The greatest increase was in primary ADT among older men with localized cancer, from 4% to 31% during this period.

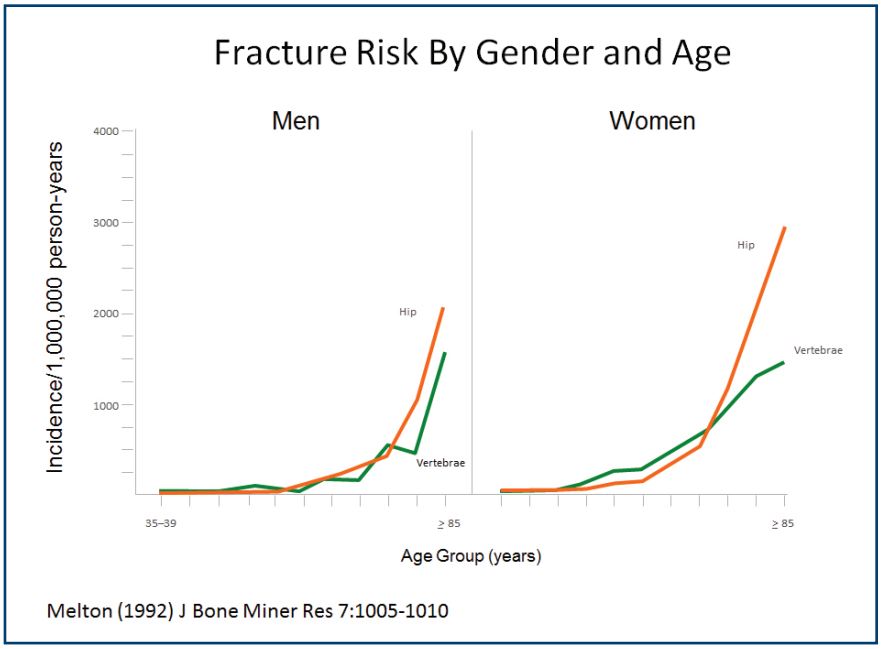
Rates of ADT vary substantially by country. In Sweden, for example, only 12% of men received ADT as primary therapy and another 12% were prescribed ADT during 10 years of follow-up.[15]

Osteoporosis and Fractures

Osteoporosis is an important but often underappreciated problem in men worldwide. In the United States, 2 million men have osteoporosis and 12 million more are at risk.[16] After age 50, one in four men has a clinical fracture. In the United States, about 80,000 men per year break a hip.

The major causes of acquired osteoporosis in men are alcohol abuse, chronic glucocorticoid

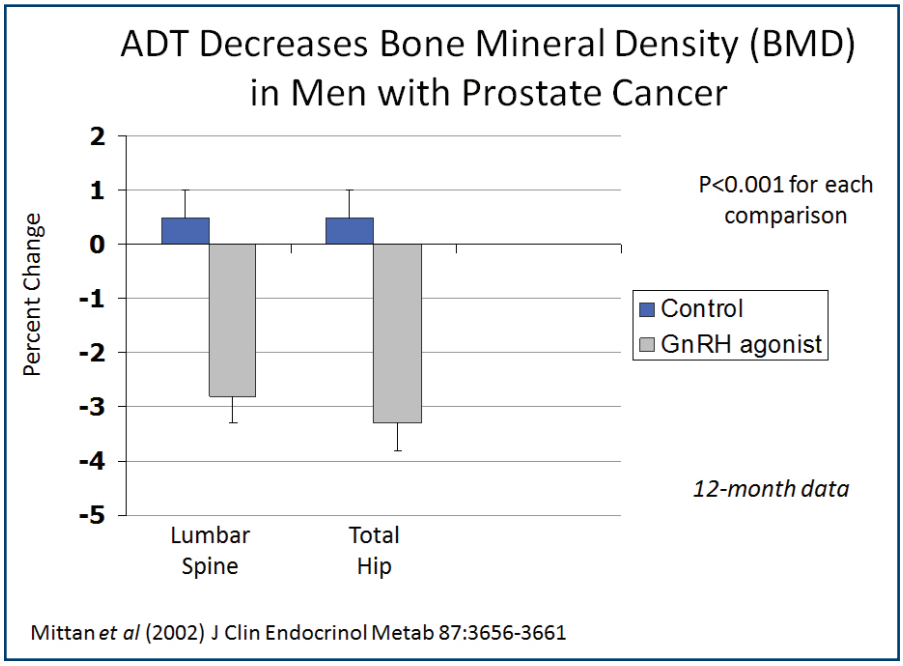
therapy and hypogonadism.[17] These causes account for approximately one half of all cases of osteoporosis in men. Smoking, low dietary calcium intake, vitamin D deficiency and sedentary lifestyle also contribute to osteoporosis risk.



Melton (1992) J Bone Miner Res 7:1005-1010

ADT is associated with greater risk for clinical fractures. In large population-based studies of men with prostate cancer, ADT was associated with 21-45% greater risk for clinical fracture.[18-20] Longer treatment durations were associated with greater fracture risk. Older age and medical co-morbidities were also associated with higher fracture rates.

ADT increases bone turnover[21] and decreases bone mineral density (BMD).[21-24] ADT decreases BMD of hip and spine by approximately 2% to 3% after one year. Most studies have reported that BMD continues to decline steadily during long-term treatment. Some, but not all, men develop osteoporosis during ADT for prostate cancer. Pre-treatment bone mineral density varies between men because of individual differences in peak bone mass and rates of adult bone loss. Accordingly, men with prostate cancer start ADT with different relative risks for developing osteoporosis. Rates of bone loss during ADT also vary between individuals.



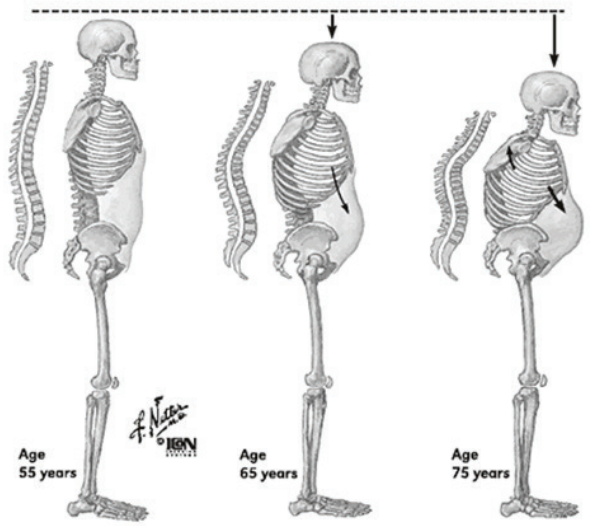
Mittan *et al* (2002) J Clin Endocrinol Metab 87:3656-3661

There are no comprehensive evidence-based guidelines for the treatment and prevention of osteoporosis in men receiving ADT for prostate cancer. In the absence of population-specific, evidence-based recommendations, we recommend use of published guidelines for the general population.

The National Osteoporosis Foundation (NOF) recommends a comprehensive approach to the evaluation and management of osteoporosis.[25] All men aged 50 years and older should be

evaluated for osteoporosis risk by detailed clinical history and physical examination. Individual fracture risk can be estimated using the World Health Organization (WHO) 10-year fracture risk model (FRAX®).[26] The clinical risk factors in this risk model include prior fragility fracture, family history of hip fracture, current tobacco smoking, chronic use of glucocorticoids, daily consumption of alcohol, rheumatoid arthritis and other conditions associated with secondary osteoporosis. When using the WHO model to estimate fracture risk in men with prostate cancer, ADT should be considered a condition associated with secondary osteoporosis.[27] The clinical risk factors included in the WHO model increase fracture risk independently of BMD and can be combined with BMD measurement to estimate an individual patient's risk for future fracture.

Osteoporosis in Men

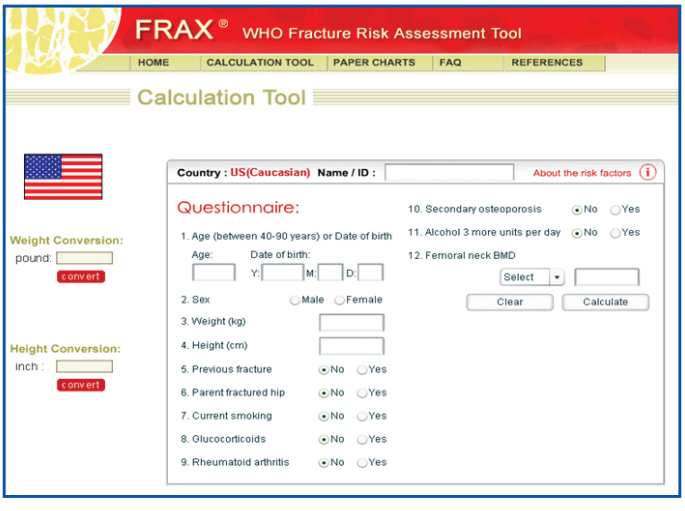


Note: Compression fractures of thoracic vertebrae lead to loss of height and progressive thoracic kyphosis (dowager's hump). Lower ribs eventually rest on ileac crests, and downward pressure on viscera causes abdominal distention.

Source: Netter 1987. Netter Illustrations used with permission from Icon Learning Systems, a division of MediMedia, USA, Inc. All rights reserved.

The Endocrine Society recommends measurement of BMD for men at increased risk for osteoporosis.[28] BMD testing is recommended for all men aged 70 years or older and for younger men (aged 50-69) with additional risk factors including hypogonadism. The Endocrine Society does not provide recommendations about the frequency of BMD testing to screen for osteoporosis in men; BMD monitoring every 1-2 years is recommended to assess the response to osteoporosis treatment.

WHO/FRAX Risk Assessment

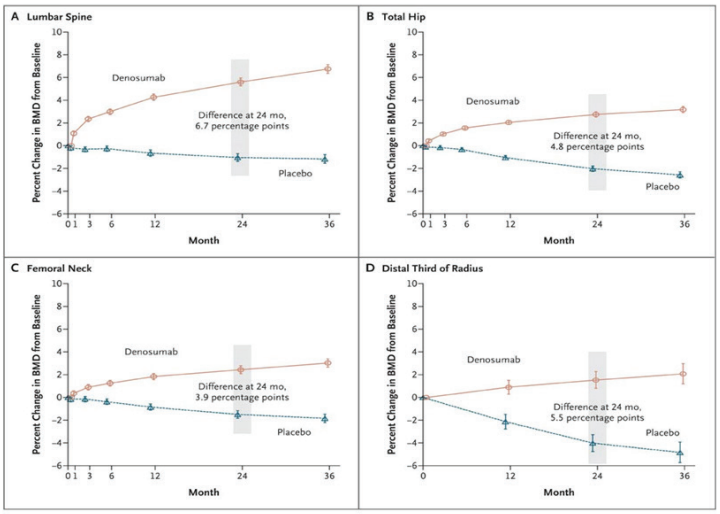


www.shef.ac.uk/FRAX/

The National Osteoporosis Foundation (NOF) recommends several interventions to reduce fracture risk in the general population.[25] These include an adequate intake of calcium and vitamin D, participation in regular weight bearing and muscle-strengthening exercise, cessation of tobacco use, identification and treatment of alcoholism and treatment of other risk factors for fracture such as impaired vision. NOF supports the Institute of Medicine (IOM) recommendations that men aged 50-70 consume 1,000 mg per day of calcium and men aged 71 and older consume 1,200 mg per day of calcium. NOF recommends an intake of 800 to 1,000 international units (IU) of vitamin D per day for adults aged 50 and older. The Institute of Medicine Dietary Reference Intakes for vitamin D are 600 IU per day until the age of 70 and 800 IU per day for adults aged 71 years and older.

The NOF recommends consideration of a marketed drug for men who are older than age 50 and at increased fracture risk based on any of the following conditions: (1) a hip or vertebral fracture, (2) T-score ≤ -2.5 at the femoral neck, total hip or lumbar spine, or (3) low bone mass (T-score between -1.0 and -2.5 at the femoral neck or lumbar spine) and a WHO 10-year probability of a hip fracture ≥3% or 10-year probability of a major osteoporosis-related fracture ≥20%.[25] The Endocrine Society recommends pharmacologic treatment for osteoporosis for men with prostate cancer receiving ADT who have a high risk of fracture.[28]

Denosumab Increased BMD at All Skeletal Sites



Smith MR et al (2009) N Engl J Med 361:745-755

Bisphosphonates (alendronate, ibandronate, risedronate and zoledronic acid) are the most commonly prescribed drugs used to treat osteoporosis in the general population. Many clinical trials have evaluated intravenous and oral bisphosphonates to prevent bone loss during ADT for prostate cancer. Randomized controlled trials of of pamidronate[21,29], zoledronic acid[30-33], alendronate[34] and risedronate[35,36] have consistently reported significant improvements in BMD. Most of these studies were small and had short followup; none was adequately designed to evaluate the effects of bisphosphonate treatment on fractures.

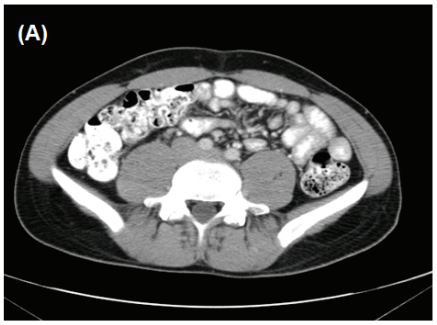
Denosumab is the only drug approved by the Food and Drug Administration (FDA) to prevent bone loss in men receiving ADT. Denosumab is a fully human IgG2 monoclonal antibody that binds to the receptor activator of nuclear factor-KB ligand (RANKL), an essential mediator of osteoclast formation, function and survival.[37] In a large, randomized controlled trial of men receiving ADT for prostate cancer who were at greater risk for clinical fractures, denosumab significantly increased BMD and reduced new fractures.

Commentary: *Strong evidence shows that ADT increases fracture risk. Older age and longer ADT duration are associated with higher fracture rates. For all men receiving ADT, we recommend regular weight-bearing exercise, adequate intake of calcium and vitamin D and individual assessment of fracture risk. We recommend drug therapy for those men with prior history of fracture, osteoporosis or clinical features consistent with an elevated fracture risk.*

Sarcopenia

Sarcopenia refers to the age-related decrease in skeletal muscle or lean body mass (LBM).[38] Sarcopenia is associated with mobility disorders, greater risk of falls and fractures, impaired ability to perform activities of daily living, disabilities, loss of independence and shorter survival.[39,40] In addition to aging, multiple other factors contribute to decreased muscle mass including poor

Abdominal Obesity and Sarcopenia during ADT



Eugonadal young man | Older man on ADT

GnRH agonist-associated sarcopenic obesity. GnRH agonists increase abdominal cross sectional area primarily through the accumulation of subcutaneous fat. Cross sectional images of a young healthy man (A) and of an obese man receiving long term GnRH agonist therapy (B). Note the relative paucity of abdominal and paraspinal musculature and the accumulation of subcutaneous fat.

Saylor PJ and Smith MR *et al* (2009) J Urol

nutrition, sedentary lifestyle, chronic diseases and certain medications.[39,41]

Androgens are important determinants of muscle mass in men. Serum testosterone concentrations correlate positively with LBM in men.[42] Testosterone replacement therapy increases muscle mass for men with hypogonadism due to aging and/or chronic disease.

ADT decreases muscle mass in men with prostate cancer. ADT decreases muscle mass by approximately 3-4% during the first year of treatment.[43] Muscle loss is greatest during initial ADT although men continue to lose muscle mass at an accelerated rate during long-term ADT.[44,45] Older men lose more muscle during short and long-term ADT than younger men.[45]

The functional consequences of muscle loss during ADT have not been adequately characterized. ADT is associated with fatigue, loss of energy, emotional distress and lower overall quality of life.[46-48] Sarcopenia may contribute to the adverse effects of ADT on physical function and quality of life.[49] Decreased muscle mass is associated with frailty and greater risk for falls in the elderly and may contribute to greater fracture risk in men receiving ADT for prostate cancer.

Little is known about the best strategy to prevent treatment-related changes in body composition. In one study, 155 men who were initiating ADT for prostate cancer were assigned to either resistance exercise training three times per week or no intervention.[50] After three months, body composition did not differ between the groups although the exercise intervention group had less fatigue, higher quality of life and higher levels of muscular fitness.

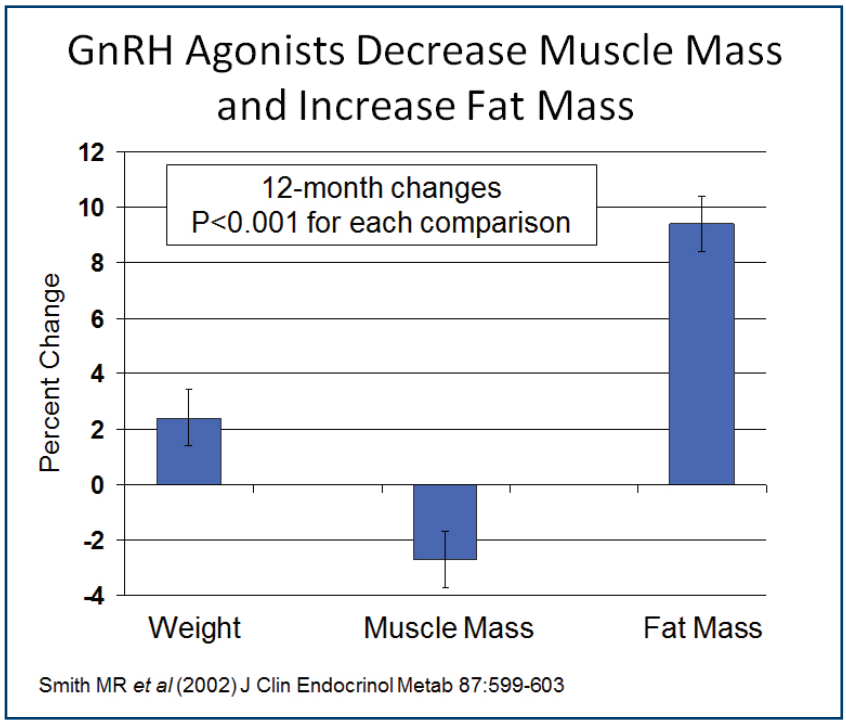
Commentary: *Strong evidence shows that ADT results in muscle loss. The effects of ADT on muscle function and physical performance have not been adequately characterized. We recommend regular weight-bearing exercise to prevent muscle loss during ADT–though there is limited information about its effectiveness.*

Obesity and Obesity-Related Metabolic Alterations

Obesity is a global epidemic. Rates of obesity (defined as body mass index (BMI) >30.0 kg/m2) have more than doubled worldwide since 1980.[51] In 2012, 34% of U.S. men were obese and an additional 38% were overweight (BMI 25 to <30.0 kg/m2).52 Rates of obesity vary across states, but no state has less than a 20% prevalence of obesity. Obesity is associated with some of the leading causes of preventable death including cardiovascular disease, type 2 diabetes and certain types of cancer.

In men with prostate cancer, ADT significantly increases body weight and fat mass.[43,44,53-55] After one year, ADT increases weight by about 3% and fat mass by about 10%.[43,44] ADT appears to preferentially increase subcutaneous rather than intra-abdominal or visceral fat mass. In one prospective study, ADT increased subcutaneous fat area by 11.1% after one year but did not change intra-abdominal fat area.[44] In another study, subcutaneous fat accounted for 94% of the observed 16.5% increase in total abdominal fat area during ADT.[56] Treatment-related increases in fat mass are apparent in as little as three months after starting ADT.[57,58] With long-term ADT, fat mass continues to increase, but at slower rate than during initial treatment.[59]

Treatment-related increases in fat mass are accompanied by metabolic alterations including insulin resistance (decreased insulin sensitivity) and increased serum cholesterol and triglycerides. Insulin resistance is a metabolic abnormality that accompanies obesity, pre-diabetes and diabetes. Insulin resistance is an independent risk factor for cardiovascular disease and is present in about one-quarter of adults in the general population.[60,61] In non-diabetic men with prostate cancer, ADT increases fasting insulin levels and decreases insulin sensitivity.[57,58,62] ADT-related decreases in insulin sensitivity are evident as soon as three months after starting ADT and appear to persist with long-term treatment.



ADT increases serum cholesterol and triglycerides. In men with prostate cancer, ADT increases total cholesterol by about 10% with similar relative increases in both HDL and LDL cholesterol after one year. ADT has more marked effects on serum triglycerides with most studies reporting increases of about 30% after one year of treatment.[63,64] Similar changes in cholesterol and triglycerides have been reported after three months of ADT.[62,65] The net effect of treatment-related alterations in serum cholesterol and triglycerides on cardiovascular disease risk in men receiving ADT for prostate cancer is unknown. The largest observed effect of ADT is an increase in serum triglycerides. After controlling for other cardiovascular disease risk factors, however, serum triglycerides are not associated with risk for cardiovascular disease in the general population.[66] ADT

modestly increases serum levels of both HDL and LDL cholesterol–changes that have directionally different effects on the risk of vascular disease in the general population. ADT has no known effects on other cardiovascular disease risk factors including blood pressure and C-reactive protein.

There are no evidence-based guidelines to prevent obesity in men receiving ADT for prostate cancer. We support the recommendations from the Centers for Disease Control and Prevention to prevent obesity in the general population (**www.cdc.gov/obesity**). These recommendations include increased physical activity, decreased intake of high calorie foods and increased consumption of fruits and vegetables.

Commentary: *Strong evidence shows that ADT increases body weight gain and fat mass. ADT is associated with obesity-related metabolic alterations including insulin resistance and increased cholesterol and triglycerides. We recommend increased physical activity and a plant-based diet to prevent treatment-related obesity and associated metabolic alterations, although there is limited information about the effectiveness of these interventions during ADT.*

Diabetes Mellitus

Diabetes is a global epidemic and a leading cause of death. Rates of diabetes have more than doubled over the past 30 years and are projected to double again by 2030. More than 350 million people have diabetes worldwide–about 90% have type 2 diabetes. In the United States, more than 9% of adults and more than 25% of seniors have diabetes; about one-quarter of cases are undiagnosed. Long-term complications of diabetes include heart disease, stroke, kidney failure, foot ulcers and loss of vision. Risk factors for type 2 diabetes include family history, non-Caucasian race, older age, obesity and sedentary lifestyle.

Observational studies have consistently reported that ADT increases the risk for diabetes. In large population-based studies of non-diabetic men with prostate cancer ADT was associated with a 16-44% increase in new diagnoses of diabetes.[49,67,68] Greater risk for diabetes was observed with short-term ADT and risk remained elevated with longer term treatment.

ADT also appears to worsen diabetes control among men with pre-existing diabetes. In a large population-based study of men with prostate cancer and diabetes, ADT was associated with a requirement for more intense medical treatment for diabetes and worse diabetes control.[69]

There are no specific evidence-based guidelines to reduce the risk of diabetes in men receiving ADT for prostate cancer. TABLE 1 summarizes the American Diabetes Association's (ADA) recommendations for the diagnosis of diabetes, testing for diabetes in asymptomatic patients and prevention/delay of type 2 diabetes in the general population.[70] Notably, testing for diabetes should be considered starting at age 45 for all men. Younger men who are overweight/obese and have one or more additional risk factors for diabetes should begin testing sooner. Men who are at risk for diabetes should be referred to a support program targeting 7% weight loss and increased physical activity to at least 150 minutes per week of moderate activity.

Commentary: *Strong evidence suggests that ADT increases the risk for diabetes. We recommend diabetes screening for all men receiving ADT. For overweight and obese men receiving ADT, we recommend weight loss and increased physical activity. Strong evidence indicates that support programs targeting 7% weight loss and increased physical activity of at least 150 minutes per week of moderate activity are effective in preventing diabetes in the general population. The effectiveness of these interventions has not been adequately evaluated during ADT.*

TABLE 1: Standards of Medical Care in Diabetes for the General Population

Criteria for Diagnosis of Diabetes

- Hemoglobin A1C ≥6.5%, OR
- Fasting plasma glucose (FPG) ≥126 mg/dL (7.0 mmol/L), OR
- Two-hour plasma glucose ≥200 mg/dL (11.1 mmol/L) during an oral glucose tolerance test (OGTT).

Testing for Diabetes in Asymptomatic Patients

- Testing to detect type 2 diabetes and prediabetes in asymptomatic people should be considered in adults of any age who are overweight or obese (BMI ≥25 kg/m2) and who have one or more additional risk factors for diabetes. In those without these risk factors, testing should begin at age 45 years.
- If tests are normal, repeat testing at least at 3-year intervals is reasonable.
- For those identified with prediabetes (hemoglobin A1C 5.7-6.45%), screening for and treatment of modifiable risk factors for cardiovascular disease is suggested. Annual monitoring for the development of diabetes is also suggested.

Cardiovascular Disease

Cardiovascular disease, including coronary heart disease, cardiovascular death, myocardial infarction and stroke, is the leading cause of death in the developed world. In the United States, cardiovascular disease causes one in every four deaths. About 8% of American men have cardiovascular disease. Key risk factors for cardiovascular disease are high blood pressure, high LDL cholesterol and smoking. Other risk factors include diabetes, being overweight or obese, poor diet, physical inactivity and excessive alcohol consumption.

Some, but not all, population-based studies have reported an association between ADT and cardiovascular disease.[67,71-73] Two large studies of American men with prostate cancer reported that ADT with a GnRH agonist was associated with an 11%-28% greater risk for myocardial infarction.[67,71] In contrast, a study of Canadian men with prostate cancer reported no association between ADT and incident myocardial infarction.[73] Other studies have also reported no association between ADT and death from cardiovascular disease.[74-80]

There are no evidence-based guidelines to reduce the risk of cardiovascular disease in men receiving ADT for prostate cancer. Existing guidelines recommend lowering blood pressure and LDL cholesterol to decrease the risk of death from cardiovascular disease in adult men and women. The American Heart Association (AHA), American College of Cardiology (ACC) and

Centers for Disease Control and Prevention (CDC) provide guidelines for treatment of high blood pressure[81] and high cholesterol.[81,82] The AHA and ACC also provide lifestyle recommendations to reduce cardiovascular disease risk for the general population (TABLE 2).[83]

Commentary: *The evidence that ADT increases the risk of cardiovascular disease is weak. Because cardiovascular disease is the leading cause of mortality in men, however, we recommend that all men with prostate cancer, regardless of ADT use, follow recommendations to reduce cardiovascular disease risk in the general population.*

TABLE 2: Summary of AHA/ACC Lifestyle Recommendations to Reduce Risk for Cardiovascular Disease in the General Population

Habits

- Don't smoke. Visit www.cdc.gov/tobacco and www.smokefree.gov for tips on quitting.

Diet

- Consume a dietary pattern that emphasizes intake of vegetables, fruits, and whole grains
- Reduce intake of saturated fats (aim for less than 6% of calories from saturated fat)
- Reduce intake of trans fat
- For men with high blood pressure, lower sodium (salt) intake

Physical Activity

- Moderate to intense aerobic physical activity, 3-4 times per week, averaging 40 minutes per session

Anemia

Anemia is defined as a decreased amount of red blood cells or hemoglobin in the blood. Symptoms of anemia are often nonspecific and may include fatigue, shortness of breath and/or poor ability to exercise. Anemia is often classified by cause (due to blood loss, decreased red blood cell production, or increased red blood cell breakdown). Anemia can also be classified based on the size, shape and amount of hemoglobin in red blood cells. Diagnosis of anemia in men is based on a hemoglobin level of less than 13 to 14 g/dL; further testing is required to determine the cause.

Androgens stimulate the synthesis of erythropoietin, a hormone that promotes the production of red blood cells. Consistent with the important role of androgens in erythropoiesis, ADT decreases red blood cell production. ADT decreases hemoglobin by an average of 1 g/dL and leads to a diagnosis of anemia in more than 90% of men.[84] Anemia associated with ADT is classified as normochromic (normal color) and normocytic (normal size). Discontinuation of ADT is usually accompanied by prompt recovery of hemoglobin and red blood cell count to pre-treatment baseline levels.

The diagnosis of anemia in men with prostate cancer may result in unnecessary testing by clinicians who are unaware of this common and expected effect of ADT. To avoid unnecessary testing, men with prostate cancer and their clinicians should be informed that ADT predictably results in mild to moderate anemia. The anemia that results from ADT is rarely associated with symptoms and rarely requires treatment. Treatment with erythropoietin increases hemoglobin

levels in men receiving ADT[84] but current guidelines recommend against its use because erythropoietin treatment is associated with greater mortality in patients with advanced cancers.[85]

Central Nervous System

Cognitive Function

In the general population of older men, low testosterone levels are associated with alterations in spatial and visual processing.[86] In contrast, studies of effects of ADT in men with prostate cancer have reported conflicting results on cognitive function. Three different studies reported that verbal memory declined, did not change and improved after ADT. In a randomized prospective study, there was no consistent adverse effect of ADT on cognitive function.[87] A meta-analysis of 14 studies concluded that men receiving ADT may experience a decline in performance on visual motor tasks but no other significant cognitive changes.[88] The observed decline in visual motor skills may be due to treatment-related muscle loss or by other unknown mechanisms.

Although studies to date have reported no consistent adverse effects of ADT on cognition, some men experience substantial cognitive changes during ADT. These cognitive changes may reflect exacerbation of pre-existing cognitive impairment, including dementia. Cancer and/or cancer therapy may release substances called inflammatory cytokines that contribute to depression, fatigue, impaired sleep and cognitive dysfunction.[89]

Pharmacologic approaches to improve cognitive function during ADT have focused on estrogen replacement. Limited evidence suggests that estradiol may positively impact some aspects of cognitive function in men and women.[90] Several small studies evaluated the effects of estradiol on cognitive function in men receiving ADT. In one study, treatment with an estrogen patch resulted in improvement in recall but not in fatigue, confusion and vigor scores.[91] In another study, low dose estradiol had no effect of cognition.[92] A third study reported that estradiol treatment failed to improve verbal memory performance compared to placebo.[93]

Preliminary evidence suggests that participation in group "cognitive rehabilitation" may improve short-term verbal memory in cancer survivors.[94] In these sessions, participants are taught techniques aimed at memory and attention difficulties, educated in habit formation, use of memory aids such as making a "to do" list and mindfulness meditation. The efficacy of cognitive rehabilitation has not been adequately evaluated in men receiving ADT.

Depression

Depression is common in men with prostate cancer and other malignancies. Depression during prostate cancer treatment is associated with higher rates of hospitalization and death.[95] ADT may contribute to risk for depression in men with prostate cancer. In a prospective study, ADT increased feelings of depression, tension, anxiety, fatigue and irritability.[96] Men with a prior history of depression are at greatest risk for diagnosis of depression during ADT.[97]

Men with a past history of depression should be closely monitored and referred to their primary care provider or a mental health provider at the first sign of depression. If anxiety and/or depression are significant, treatment with an antidepressant may be indicated and, in some cases, prophylactic use might be considered. Sleep disturbance, sometimes related to nocturnal hot flashes, may worsen depression. Use of an anti-depressant may treat both depression and hot

flash symptoms. Cognitive behavioral therapy and mindfulness-based stress reduction can be useful adjuncts to, or substitutes for, medication.

Fatigue

Fatigue is one of the most commonly reported symptoms in men receiving ADT. Fatigue is a subjective feeling of tiredness. In contrast to tiredness associated with inadequate rest, fatigue is not alleviated by periods of sleep. More than 90% men receiving long-term ADT report some degree of fatigue and almost one-half report fatigue that interferes with normal daily function.[98] Some men report decreased initiative and/or motivation during treatment; the term fatigue appears to inadequately characterize to these adverse effects of ADT.

Several prospective clinical studies have reported that regular physical exercise decreases fatigue during ADT.[50,99-101] Exercise may also mitigate some of the other adverse effects of ADT including muscle loss, obesity, sexual dysfunction and psychological distress.

Sexuality

ADT uniformly results in sexual dysfunction. While surgery and radiation are associated primarily with erectile dysfunction, ADT causes both erectile dysfunction and decreased libido or sexual interest. Most men receiving ADT report lower internal drive to seek for sexual stimuli, lower sexual response to visual and tactile stimuli and inability to attain orgasm.[102]

There is a common misconception that decreased sexual interest during ADT alleviates the distress from sexual dysfunction. Sexual dysfunction is stressful for many patients and their partners, especially if they are poorly informed about the adverse effects of ADT. Men are often reluctant to discuss their sexual interest and performance, even with their partner, and this reticence may result in withdrawal of both emotional and physical intimacy.[103] Loss of libido may have an adverse impact on a masculine self-image that may already be impaired by reduced penile length and testicular volume, increased body weight, decreased muscle mass and strength and emotional liability.

Clinicians should evaluate sexual interest and ability prior to initiation of ADT. In two studies of men with prostate cancer, only 25-50% of men were sexually active prior to starting ADT.[104] For men interested in maintaining sexual interest and ability during treatment, four steps are important:[102]

1) Try to optimize ADT to reduce the burden of sexual side effects. When medically appropriate, consider shorter treatment duration and/or intermittent ADT as a strategy to mitigate adverse effects. Alternative forms of ADT may be appropriate for some men.

2) Men should be encouraged to experience alternative approaches to maintain or recreate intimacy and sexual interest. Improved communication between partners, an open mind and an optimistic attitude may help improve sexuality during treatment.

3) Consider referring motivated men for professional psycho-sexual support.

4) Advise men about specific therapies and preventive measures. Injection therapy and vacuum devices are more likely to be effective for erectile dysfunction during ADT than phosphodiesterase inhibitors (examples: sildenafil, tadalafil, vardenafil).

Physical activity may also help improve sexual function during ADT. In a small randomized

controlled trial, for example, more men assigned to a supervised exercise program reported a major interest in sex than those assigned to a control group (17% versus 0%).[101]

Exercise and Nutrition

Exercise is strongly associated with improved health outcomes in the general population. In observational studies of adults, regular physical activity is linked to lower risk for cardiovascular diseases, diabetes, hypertension, obesity, osteoporosis, anxiety, decline in cognitive function, depression and a variety of cancers.[105]

Exercise also appears to improve the health of men receiving ADT. A 2014 review of 10 prospective exercise intervention studies reported that exercise was associated with improvements in quality of life, fatigue, physical function, muscular strength, cardiorespiratory fitness and muscle mass in men receiving ADT.[106] Three subsequent prospective randomized studies reported similar benefits of exercise during ADT.[107-109] In one study of men starting ADT, an intervention combining aerobic and resistance training improved sexual function, social functioning and mental health.[107]

Less is known about the role of nutrition on health outcomes during ADT for prostate cancer. Several of the reported prospective studies included nutritional interventions in additional to exercise but were not designed to evaluate the specific role of nutrition on outcomes during ADT.

Commentary: *Strong evidence suggests that exercise improves health outcomes during ADT. Little is known about the optimal type, intensity and duration of physical activity to prevent adverse effects of ADT. Based on guidelines developed for the general population, we recommend that men increase physical activity to at least 150 minutes per week of moderate activity. This recommendation may need to be individualized for men with physical limitations or certain medical problems including cardiovascular disease. The PCF monograph entitled "Nutrition, Exercise and Prostate Cancer" provides additional specific recommendations about nutrition and exercise for men with prostate cancer.*

New Androgen Pathway Inhibitors

Most men with metastatic prostate cancer eventually experience disease progression despite continuous ADT, a disease state termed castration-resistant prostate cancer (CRPC). In recent years, multiple new drugs have been approved to treat men with metastatic CRPC. Two of these new drugs, abiraterone acetate (Zytiga®) and enzalutamide (Xtandi®), are classified as hormonal agents. Abiraterone acetate inhibits androgen biosynthesis and further lowers serum testosterone levels to less than 1 ng/dL. In contrast, enzalutamide inhibits the androgen receptor. Both drugs improve progression-free and overall survival in men with metastatic CRPC. Both abiraterone acetate and enzalutamide are described as well tolerated although there is limited information about the potential long-term effects of these agents on obesity, sarcopenia and risks for diabetes and fractures. By further lowering serum testosterone levels or blocking the action of serum androgen, it is plausible that these agents may worsen the severity of the recognized adverse effects of ADT and/or result in previously unrecognized harms of severe androgen deficiency.

Knowledge Gaps and Future Research Needs

The work of the writing group served the added purpose to identify important gaps in knowledge about maintaining health during androgen deprivation therapy. Additional research is needed to address the following key questions:

- What are the functional consequences of muscle loss during long-term ADT?
- What are the effects of the new androgen pathway inhibitors on prostate cancer survivors? Do these drugs worsen the typical adverse effects of ADT and/or cause previously unrecognized harms?
- What factors influence the severity of treatment-related adverse effects?
- Do the adverse effects of ADT change over time?
- What is the comparative effectiveness for different exercise interventions?
- What is the comparative effectiveness of different nutritional interventions?
- What can be done to improve compliance with lifestyle interventions?
- Is there a role for cognitive rehabilitation for men receiving ADT?
- What are the differences in the adverse effects of different forms of ADT?
- What are the roles of complementary medicines and practices to mitigate adverse effects of ADT?
- Are there biomarkers that can reliably predict risk for adverse effects?

Summary Recommendations: Maintaining Health during Androgen Deprivation Therapy

ADT improves prostate cancer outcomes in some settings but has potential adverse effects. These adverse effects include increased risk for a variety of age-related medical problems including osteoporosis, obesity, sarcopenia and diabetes. Although it is unclear whether ADT increases risk for cardiovascular disease, all men with prostate cancer should follow recommendations to reduce risk because cardiovascular disease is the leading cause of mortality in the general population. Using the best available evidence, this summary provides a core action plan for prostate cancer survivors to maintain health during ADT.

Testing and Diagnosis

Osteoporosis

Age and other factors including prior fracture, smoking, alcohol use and family history of hip fracture explain most of an individual's risk for fracture. Estimate your fracture risk using the online FRAX® risk assessment tool (www.shef.ac.uk/FRAX). Bone mineral density measurement with a DXA scan may provide additional information about your fracture risk.

Obesity

Overweight/obesity is the major and most controllable risk factor for diabetes, as well as a risk factor for cardiovascular disease. Calculate your body mass index (BMI) using your measured height and weight and a BMI calculator (www.nhlbi.nih.gov/health/educational/lose_wt). BMI categories: normal weight = BMI 18.5-25 kg/m2, overweight = BMI 25-29.9 kg/m2 and obese = BMI >30 kg/m2.

Diabetes

All men should have diabetes screening with the hemoglobin A1C blood test. Hemoglobin A1C categories: normal = A1C <5.7%, pre-diabetes = A1C 5.7-6.4%, diabetes >6.5%. If hemoglobin A1C is normal, repeat testing at least every 3 years.

Cardiovascular Disease

The major controllable risk factors for cardiovascular disease are high blood pressure, high LDL cholesterol and smoking. All men should have screening for high blood pressure and cholesterol. Blood tests for cholesterol should be performed at least every five years.

Healthy Lifestyle

Lifestyle changes that promote general health may also reduce your risks for adverse effects of ADT.

Healthy Habits

- Stop tobacco use
- Limit alcohol intake

Healthy Nutrition

- Increase consumption of vegetables and fruits, including calcium-rich plants
- For overweight and obese men, start a support program targeting 7% weight loss

Exercise

- Increase physical activity to at least 150 minutes per week of moderate activity to prevent/treat obesity and reduce risks for diabetes and cardiovascular disease
- Increase weight bearing exercise to reduce fracture risk
- Resistance exercise training may prevent muscle loss

See PCF Monograph entitled *"Health and Wellness: Living with Prostate Cancer"* for additional diet and lifestyle recommendations. (www.pcf.org/guides)

Supplements and Medications

- Vitamin D 600-1,000 IU daily to prevent bone loss
- For men with prior history of fracture, osteoporosis or an elevated fracture risk based on FRAX, consider treatment with a marketed drug to prevent fractures.
- Statins are the mainstay of treatment for elevated cholesterol.

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