HORMONES 2017, 16(2):115-123

Review

Adverse effects of androgen deprivation therapy in patients with prostate cancer: focus on metabolic complications

Vasileios Tzortzis,[1] Michael Samarinas,[1] Ioannis Zachos,[1] Athanasios Oeconomou,[1] Louis L. Pisters,[2] Alexandra Bargiota[3]

[1]Department of Urology, Faculty of Medicine, School of Health Sciences, University of Thessaly, Larissa, Greece, [2]Department of Urology, Division of Surgery, The University of Texas MD Anderson Cancer Center, Houston, TX, USA, [3]Department of Endocrinology and Metabolic Diseases, Faculty of Medicine, School of Health Sciences, University of Thessaly, Larissa, Greece

ABSTRACT

Prostate cancer is the most common cancer among men and androgen deprivation therapy (ADT) is the most effective treatment for this disease. The cornerstone of the treatment of prostate cancer is inhibition of testosterone production which interrupts testosterone-induced growth of the prostate tumor. The dramatic decrease in testosterone levels, however, has several undesirable effects on the metabolic profile and bone metabolism and can also lead to fatigue, loss of libido, gynecomastia, and anemia, provoke vasomotor flushing, and generally affect the quality of life. Due to the long-term survival rates of patients with prostate cancer, treatment-related adverse effects are highly relevant and thus, in each clinical setting, the benefits of ADT must be weighed against treatment-related adverse effects. The current review focuses on the more recently described metabolic complications of androgen deprivation therapy, including obesity, diabetes, lipid alterations, metabolic syndrome, and cardiovascular disease. In addition, it provides practical management recommendations drawn from the available guidelines issued by the American Diabetes Association and American Heart Association.

Key words: Androgen deprivation therapy, Diabetes, Metabolic complications, Prostate cancer

INTRODUCTION

Prostate cancer is the most common cancer among men, with a median age at diagnosis of 68 years. Effective systematic treatments of prostate cancer have greatly improved life expectancy for these patients and, with the exception of patients with metastatic disease, the 5-year relative survival rate is today 98.8%.[1]

Androgen deprivation therapy (ADT) is the cornerstone treatment for men with prostate cancer (PCa), inhibiting testosterone production and interrupting testosterone regulation of the prostate tumor. It is estimated that 50% of men with prostate cancer will undergo ADT at some point of their treatment.[2] ADT improves the 10 years' overall survival rate by up

Address for correspondence:
Tzortzis Vasileios, University of Thessaly, School of Health Sciences, Faculty of Medicine, Larissa, Greece;
E-mail: tzorvas@otenet.gr

Received: 30-03-2017, Accepted: 03-04-2017

to 26% in patients with localized and locally advanced disease when administered in combination with external beam radiation therapy,[3,4] though in men with metastatic disease it contributes mainly to pain management.[5-7]

The aim of ADT is hypogonadism, which is achieved either surgically with bilateral orchiectomy or medically using LHRH agonists or antagonists. LHRH analogues initially stimulate pituitary receptors, causing a temporary rise in LH and FSH, but chronic exposure leads to the down-regulation of LHRH-receptors and decrease of LH, FSH, and testosterone. LHRH antagonists bind immediately and competitively to LHRH receptors in the pituitary gland, resulting in a rapid hormonal decrease.[8-10] However, the dramatic decrease in testosterone levels can have several undesirable effects on the metabolic profile and bone metabolism, leading to fatigue, loss of libido, gynecomastia and anemia, causing vasomotor flushing and affecting the quality of life.[11] Due to the long-term survival rate of patients with prostate cancer, treatment-related adverse effects are highly relevant and thus, in each clinical setting, the benefits of ADT must be weighed against treatment-related adverse effects.

The current review focuses on the more recently described metabolic complications of androgen deprivation therapy including obesity, diabetes, lipid alterations, metabolic syndrome, and cardiovascular disease. In addition, it provides practical management recommendations drawn from available guidelines issued by the American Diabetes Association (ADA) and American Heart Association (AHA).

ADT AND OBESITY

Androgens are important determinants of body composition in men, promoting growth of lean mass and suppressing fat deposition.[12] Epidemiological studies have observed a bidirectional relationship between low testosterone levels and obesity.[13] Obesity is the single most powerful predictor of low testosterone levels in men, and low levels of testosterone and SHBG can predict accumulation of intra-abdominal fat, development of central obesity, and increased risk of metabolic syndrome.[14]

Several studies have shown that in men on ADT, body weight and body composition changes occur mainly during the first year of treatment and subsequently continue for 1 to 2 years.[15] It has been reported that weight gain after a year on treatment is about 1.5-4 k and it seems to be greater in younger patients (<65 years of age) and in non-obese patients (BMI <30Kg/m^2).[15] Changes in body composition also occur early, with an increase in total body fat of up to 10% and a reduction in lean body mass of 2.7%.[16] The fat accumulation is mainly subcutaneous, although both visceral and subcutaneous fat accumulations have been observed. Subcutaneous fat accumulation represents 94% of the total abdominal fat gained during the treatment.[15] On the other hand, reduced muscle mass can result in reduced muscle strength and produce weakness and fatigue.[17] The term sarcopenic obesity is used in the literature to describe the increase of abdominal obesity accompanied by reduced muscle mass in men undergoing ADT[18] and is found to be associated with an increase in all-cause mortality.[19]

The underlying mechanisms of increased abdominal fat with ADT are not well understood. Visceral adipocytes are known to have androgen receptors and it has been proposed that testosterone might be directly involved in fatty acid mobilization.[20] Changes in fat distribution during ADT may be due to loss of androgen-mediated inhibition of stem cell differentiation into adipocytes.[21] It has also been suggested that accumulation of visceral fat in these men could be due to reduced lipolysis as a result of the low testosterone levels.[22]

No evidence-based prevention or treatment strategies currently exist for ADT-associated changes in body composition. However, there is strong evidence concerning men with advanced disease on ADT which suggests that physical exercise is efficacious in improving cancer-specific quality of life, fatigue, and exercise capacity.[23] In the Culos-Reed study, patients who increased their physical activity had positive changes in girth measurements and blood pressure.[24] Additionally, there is evidence indicating that a 6-month combined aerobic and resistance exercise program has a significant favorable impact on resting fat oxidation, glucose, and body composition despite parallel treatment with ADT.[25]

ADT, INSULIN RESISTANCE, AND DIABETES

It is well established today that low testosterone levels in men are associated with insulin resistance and type 2 diabetes. In fact, there is a complex and multiparametric correlation between testosterone deficiency and obesity, which represents a risk factor for cardiovascular disease.[26,27] Furthermore, studies have shown that testosterone replacement improves insulin sensitivity and glycemic profiles in hypogonadal men.

Evidence concerning insulin sensitivity in patients receiving ADT is limited and the studies are quite heterogeneous as to design (different types of ADT, presence or absence of control group, short and long duration, etc.) and the results are conflicting. Nevertheless, it seems that ADT decreases insulin sensitivity in non-diabetic men within 12 weeks of initiating treatment.[18,22,28,29] The exact mechanism by which ADT increases insulin resistance is not yet clearly understood. The observed increase in fat mass, and particularly in the abdomen, in these men is thought to contribute to the reduced insulin sensitivity. Moreover, it has been speculated that certain pro-inflammatory adipokines such as TNF-a, IL-6, and resistin are increased in patients on ADT and might play a role in insulin resistance.[30,31]

Although insulin resistance appears early in men undergoing ADT, it seems that fasting hyperglycemia and frank diabetes need a year or more to develop. However, randomized studies on this subject are lacking.

Data from the Surveillance Epidemiology and End Results (SEER) database including 73,196 men with local or locoregional prostate cancer treated with LHRH agonists (36%) or orchiectomy (7%) reported a higher diabetes incidence (adjusted hazard ratio 1.42) in these men.[32] The results from the Canadian database analysis of 20,000 men are similar.[33] Keating et al in an observational study of 14,597 veterans also found that treatment with LHRH agonists was associated with a statistically significant increased incidence of diabetes.[34] Recently, a retrospective cohort study of 12,191 men diagnosed with localized prostate cancer showed that ADT may increase diabetes risk by 60%.[35] Additionally, it has been found that ADT might worsen glycemic control and increase glycosylated hemoglobin levels in patients with pre-existing diabetes.[36,37]

As the risk for diabetes development during ADT is high, the need for diabetes screening among men with prostate cancer under long-term treatment is obvious. In the absence of evidence-based recommendations, risk-adapted screening and intervention according to the guidelines from the ADA may be applied to this specific population.[38] Screening men at baseline and again in a year for those treated with long-term ADT and using fasting plasma glucose and hemoglobin A1c as screening tests seem reasonable. Individuals with hemoglobin A1c between 6.0% and 6.5% or impaired fasting glucose (fasting glucose, 100-125 mg/dL) should be considered to be at high risk for developing diabetes and need to be counseled to lose weight and undertake moderate physical activity.[39] In those with pre-existing diabetes, intensification of their hypoglycemic treatment and a more frequent follow-up might be necessary, depending on their blood glucose and HbA1c levels.

ADT AND DYSLIPIDEMIA

Several studies have documented changes in the lipid profile of men on ADT, but the results are not consistent and depend on the duration of treatment and the method used for ADT.[40] Also, in some studies the number of subjects studied was small. Although the findings are not universal, ADT seems to increase total cholesterol, LDL, HDL, and triglyceride levels.[22,40-42] Studies have demonstrated a significant increase in triglycerides levels (by about 26%), in total cholesterol (by about 10%), and in HDL (by approximately 8%-10 %), but no change in LDL levels, after 3, 6, and 12 months of ADT.[22,42,43] On the other hand, prospective studies have shown an increase in LDL, total cholesterol, and triglyceride levels with or without any changes on HDL levels.[16,28]

Hyperinsulinaemia could be responsible for some of the alterations in the lipid profile of men receiving ADT but it cannot explain the changes in HDL cholesterol. Therefore, some other factors might be involved, such as the observed increase in adiponectin levels in these patients. Adiponectins are considered to be atherothrombotic risk factors in obese subjects, being related to hemostatic markers and common carotid wall thickness.[44] However, the effect of these changes on cardiovascular risk is unknown and further studies

are needed to establish this relationship.[22,42] However, for patients undergoing ADT, diet and lifestyle changes are recommended as first-line interventions if hyperlipidemia is present in order to achieve LDL concentrations at the target level. If these measures fail, drug therapy with statins is recommended.[45] Recently, selective estrogen receptor modulators (SERMs), which are used for their effects on bone mineral density (BMD) and fracture prevention in men on ADT, have been found to affect serum lipid levels as well. In a randomized, placebo-controlled trial, toremifene was given for fracture prevention to men on ADT, and the planned interim analysis at one year exhibited a decrease in LDL cholesterol and triglyceride levels and an increase in HDL levels in the tamoxifen group.[46]

ADT AND HYPERTENSION

In a recent systematic review of studies in hypogonadal men low testosterone levels were well correlated with hypertension.[47] Hypogonadism is the key finding in men undergoing ADT, but only a few studies have examined its effect on blood pressure. The results of these studies are conflicting, with some studies showing no effect and others showing an increase in blood pressure after a year on ADT.[48,49]

ADT AND METABOLIC SYNDROME

Metabolic syndrome is a cluster of conditions, such as abdominal obesity, high triglyceride level, low HDL cholesterol level, high blood pressure, and high fasting blood sugar, that raise the risk for heart disease. Three out of these five main factors are needed for a diagnosis of metabolic syndrome and its prevalence in the adult population is estimated at about 20-25%.[50] Male hypogonadism is an independent risk factor for metabolic syndrome, while low testosterone and SHBG levels can predict metabolic syndrome in men.[51,52] Additionally, as mentioned above, ADT causes a high degree of alteration in the metabolic parameters and thus it is possible that ADT increases the risk of metabolic syndrome. Indeed, some studies have shown that about 36-55% of men receiving ADT for more than a year will develop metabolic syndrome, independent of age, race, and stage of PCa.[41,53,54] A recent meta-analysis including nine observational studies[50] and a cohort study[35] found an even higher incidence of metabolic syndrome, of up to 60-75%, in this population.

As noted above, an increase in adiposity and visceral adiposity, elevated hepatic lipolysis, and insulin resistance and an increase in pro-inflammatory factors might contribute to the development of metabolic syndrome during ADT. Additionally, it has been found that the CAG repeat polymorphism within the androgen receptor (AR) gene can also play a role in the development of metabolic syndrome. There is an inverse relationship between the length of the CAG repeat in the AR and its transcriptional activity on testosterone target genes.[55] Some studies even suggest that serum levels of testosterone can be correlated with the CAG repeat of AR, pointing to the negative-feedback loop mediated by AR to regulate testosterone levels.[56,57] The polymorphism of AR CAG repeats is reported to influence insulin sensitivity and components of metabolic syndrome in men. These findings provide additional support for the critical role of AR in androgen/AR signaling in the regulation of metabolism.[58,59]

Metabolic syndrome due to ADT has some differences to the classically defined metabolic syndrome. In classic metabolic syndrome, HDL is decreased by about 5%, while an increase in HDL is observed in the type associated with ADT.[16,48] Metabolic syndrome is related to low adiponectin levels[60] and increased C-reactive protein levels,[28] while in patients on ADT adiponectin levels are increased and C-reactive protein levels are unchanged.[61,62] The clinical significance of these differences is yet to be defined.

Finally, one must keep in mind that ADT might worsen pre-existing metabolic syndrome in these high-risk patients. Thus, screening for metabolic abnormalities before the initiation of ADT as well as close follow-up and appropriate treatment depending on the presence and the severity of the metabolic changes are essential.

ADT AND THE RISK OF CARDIOVASCULAR DISEASE

The increased rates of obesity, insulin resistance, diabetes, hyperlipidemia, and metabolic syndrome

observed in patients on ADT would support the hypothesis of a similar effect on cardiovascular disease (CVD) disease.[63] Moreover, this hypothesis might well be strengthened by recent findings indicating that several biological mechanisms induced by ADT, such as increased inflammation, atherogenic plaque formation, and plaque destabilization, could further promote CVD development in these patients.[64]

Large randomized control trials are lacking and the existing evidence regarding CVD morbidity and mortality for patients receiving ADT is rather controversial. Data from observational studies indicate overall a positive relationship between ADT and CVD. In a large population-based cohort study of 185,106 men, it was found that ADT was independently associated with an increased risk of myocardial infarction (MI) and diabetes.[65] A retrospective analysis, however, using data from the Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) and including men with prostate cancer treated with radical prostatectomy followed or not with ADT found a significant correlation of ADT with increased CV mortality, but only among patients over 65 years old (p=0.002).[66] Furthermore, a recent meta-analysis of randomized controlled trials and observational studies showed that antiandrogen was associated with a 30% decreased risk for myocardial infarction compared to GnRH agonists, while combined androgen blockade was associated with a 10% increased risk for stroke when compared to antiandrogen.[67]

In the Radiation Therapy Oncology Group (RTOG) study protocol 85-31,[68] patients with advanced prostate cancer who had either radiotherapy alone or in combination with indefinite ADT were enrolled and demonstrated no statistically significant difference regarding mortality related to CVD between the two groups (p=0.17). The RTOG trial 86-10[69] involved patients with locally advanced prostate cancer who had received a 4-month scheme of ADT plus radiation treatment (RT) versus those who had RT alone. Again, there was no statistical difference between the treatment groups as regards CV mortality (p=0.32). The RTOG protocol 92-02[70] also included patients with locally advanced prostate cancer, but both groups received ADT in addition to RT (28 months and 4 months). As above, there was no significant difference in CV mortality between the two groups (p=0.58). All these results were fully supported by a meta-analysis of eight randomized control trials (RCTs) of ADT versus no or delayed ADT in patients with non-metastatic prostate cancer which showed that sudden death due to CVD in patients receiving ADT was not different to those with no or delayed therapy.[71] Similar findings were reported in the European Organization for Research and Treatment of Cancer (EORTC) analysis.[72]

Preexisting comorbidities and different duration of the ADT could explain the observed result discrepancy among the studies. Comorbidities are important independent prognostic factors for patients with cancer and the inclusion of the existing comorbidities in hospital-based cancer registries will increase the value and use of observational research.[73]

Regarding LHRH antagonists, Smith et al[74] found that the use of degarelix in ADT for prostate cancer did not affect the CV events in the overall population (p=0.45), although in the subgroup of patients with underlying CV disease the incidence of those events was increased significantly after the use of degarelix (p=0.0013). In Albertsen's reanalysis of six RCTs, degarelix was shown to be superior to leuprolide, being associated with fewer CV events in patients with or without coexisting CVD (p=0.016 and p=0.025, respectively).[75] These studies appear to point to LHRH antagonists as an ideal alternative in ADT for high-risk patients with CVD.

It is well known that in the general population, individuals with reduced risk factors for cardiovascular disease have a lower incidence of heart disease and stroke[76] and, although strong data on ADT-attributable risk for cardiovascular events and mortality are inconsistent, the use of the AHA guidelines can be considered in this population. According to these guidelines, primary prevention should feature total tobacco cessation and appropriate management of hypertension. Low-dose aspirin is recommended for men with a 10% or greater 10-year risk for coronary heart disease. Lifestyle modification should feature weight control and low intake of saturated fat and cholesterol. If such modifications fail to achieve target LDL, statins should be used as first-line drug treatment of hyperlipidemia.[77]

Regular physical activity could be a key factor for the prevention of CVD in prostate cancer patients.

More specifically, exercise interventions that apply sound aerobic and resistance training principles should be suggested as being quite effective.[78,79] In fact, all exercise programs are likely to reduce fatigue and enhance vitality, especially among patients with the highest levels of fatigue and lowest vitality. Men with prostate cancer could improve their strength, physical functioning, and cardiovascular health by increasing their physical activity.[80,81] Finally, physical exercise significantly improves QoL, although it is not entirely clear whether it affects metabolic risk factors in patients with androgen deprivation therapy-treated prostate cancer.[82]

CONCLUSION

It is now well established that ADT improves survival in men with prostate cancer, but this benefit comes at the cost of harmful metabolic changes such as obesity, insulin resistance and diabetes, dyslipidemia and cardiovascular disease. Patients need to be well informed about these risks and the potential benefits of therapy should be carefully considered before ADT begins. Optimal management for these metabolic changes has not as yet been defined. Increase of physical activity, weight loss, and lifestyle changes are very important for the management of these metabolic aberrations of patients on ADT and should be recommended to all patients undergoing ADT. Further studies focusing on an ideal strategy of patient selection for ADT and on an optimal way for treating ADT side effects are needed.

REFERENCES

1. Ryan CJ, Small EJ, 2005 Early versus delayed androgen deprivation for prostate cancer: new fuel for an old debate. J Clin Oncol 23: 8225-8231.
2. Shahinian VB, Kuo Yf, Freeman JL, Orihuela E, Goodwin JS, 2005 Increasing use of gonadotropin releasing hormone agonists for the treatment of localized prostate carcinoma. Cancer 103: 1615.
3. Heidenreich A, Bastian PJ, Bellmunt J, et al, 2014 EAU guidelines on prostate cancer. part 1: screening, diagnosis, and local treatment with curative intent-update 2013. Eur Urol 65: 124-137.
4. Bolla M, Collette L, Blank L, et al, 2002 Long term results with immediate androgen suppression and external irradiation in patients with locally advanced prostate cancer (an EORTC study): a phase III randomized trial. Lancet 360: 103-106.
5. Messing EM, Manola J, Yao J, et al, 2006 Immediate versus deferred androgen deprivation treatment in patients with node-positive prostate cancer after radical prostatectomy and pelvic lymphadenectomy. Lancet Oncol 7: 472-479.
6. Huggins C, Hodges CV, 1941 Studies on prostate cancer: II. The effects of castration on advanced carcinoma of the prostate gland. Arch Surg 43: 209-233.
7. Heidenreich A, Bastian PJ, Bellmunt J, et al, 2014 EAU guidelines on prostate cancer. Part II: Treatment of advanced, relapsing, and castration-resistant prostate cancer. Eur Urol 65: 467-479.
8. Eisenberger MA, Blumenstein BA, Crawford ED, et al, 1998 Bilateral orchiectomy with or without flutamide for metastatic prostate cancer. N Engl J Med 339: 1036-1042.
9. Rosario DJ, Davey P, Green J, 2016 The role of gonadotrophin-releasing hormone antagonists in the treatment of patients with advanced hormone-dependent prostate cancer in the UK. World J Urol 34: 1601-1609.
10. Albertsen P, 2009 Androgen deprivation in prostate cancer-step by step. N Engl J Med 360: 2572-2574.
11. Sharifi N, Gulley J, Dahut W, 2005 Androgen deprivation therapy for prostate cancer. JAMA 294: 238-244.
12. Finkelstein JS, Lee H, Burnett-Bowie SA, et al, 2013 Gonadal steroids and body composition, strength, and sexual function in men. N Engl J Med 369: 1011-1022.
13. Allan CA, McLachlan RI, 2010 Androgens and obesity. Curr Opin Endocrinol Diabetes Obes 17: 224-232.
14. Brand JS, van der Tweel I, Grobbee DE, Emmelot-Vonk MH, van der Schouw YT, 2011 Testosterone, sex hormone-binding globulin and the metabolic syndrome: a systematic review and meta-analysis of observational studies. Int J Epidemiol 40: 189-207.
15. Smith MR, Lee H, Fallon M, Nathan DM, 2008 Adipocytokines, obesity and insulin resistance during combined androgen blockade for prostate cancer. Urology 71: 318-322.
16. Smith MR, Finkelstein JS, McGovern FJ, et al, 2002 Change in body composition during androgen deprivation therapy for prostate cancer. J Clin Endocrinol Metab 87: 599-603.
17. Stone P, Hardy J, Huddart R, et al, 2000 Fatigue in patients with prostate cancer receiving hormone therapy. Eur J Cancer 36: 1134-1141.
18. Zamboni M, Mazzali G, Fantin F, Rossi A, Di Francesco V, 2000 Sarcopenic obesity: a new category of obesity in the elderly. Nutr Metab Cardiovasc Dis 18: 388-395.
19. Simiao Tian and Yang Xu, 2016 Association of sarcopenic obesity with the risk of all-cause mortality: A meta-analysis of prospective cohort studies. Geriatr Gerontol Int 16: 155-166.
20. Reis C, Liberman S, Pompeo AC, Srougi M, Halpern A, Filho WJ, 2009 Body composition alterations, energy expenditure and fat oxidation in elderly males suffering from prostate cancer, pre- and post-orchiectomy. Clinics

(Sao Paulo) 64: 781-784.
21. Chazenbalk G, Singh P, Irge D, Shah A, Abbott D, Dumesic D, 2013 Androgens inhibit adipogenesis during human adipose stem cell commitment to preadipocyte formation. Steroids 78: 920-926.
22. Smith JC, Bennett S, Evans LM, et al, 2001 The effects of induced hypogonadism on arterial stiffness, body composition, and metabolic parameters in males with prostate cancer. J Clin Endocrinol Metab 86: 4261-4267.
23. Bourke L, Smith D, Steed L, et al, 2016 Exercise for men with prostate cancer: A systematic review and meta-analysis. Eur Urol 69: 693-703.
24. Culos-Reed SN, Robinson JW, Lau H, 2010 Physical activity for men receiving androgen deprivation therapy for prostate cancer: benefits from a 16-week intervention. Support Care Cancer 18: 591-599.
25. Wall BA, Galvão DA, Fatehee N, 2017 Exercise Improves V̇O2max and Body Composition in ADT-treated Prostate Cancer Patients. Med Sci Sports Exerc [Epub ahead of print].
26. Traish AM, Zitzmann M, 2015 The complex and multifactorial relationship between testosterone deficiency (TD), obesity and vascular disease. Rev Endocr Metab Disord 16: 249-268.
27. Ullah MI, Washington T, Kazi M, Tamanna S, Koch CA, 2011 Testosterone deficiency as a risk factor for cardiovascular disease. Horm Metab Res 43: 153-164.
28. Dockery F, Bulpitt CJ, Agarwal S, Donaldson M, Rajkumar C, 2003 Testosterone suppression in men with prostate cancer leads to an increase in arterial stiffness and hyperinsulinemia. Clin Sci (London) 104: 195-201.
29. Keating NL, O Malley AJ, Smith MR, 2006 Diabetes and cardiovascular disease during androgen deprivation therapy for prostate cancer. J Clin Oncol 24: 4448-4456.
30. Hotamisligil GS, Spiegelman BM, 1994 Tumor necrosis factor α: a key com- ponent of the obesity-diabetes link. Diabetes 43: 1271-1278.
31. Cutolo M, Sulli A, Capellino S, et al, 2004 Sex hormones influence on the immune system: basic and clinical aspects in autoimmunity. Lupus 13: 635-638.
32. Smith RM, 2008 Androgen deprivation therapy and risk for diabetes and cardiovascular disease in prostate cancer survivors. Curr Urol Rep 9: 197-202.
33. Alibhai SM, Duong-Hua M, Sutradhar R, et al, 2009 Impact of androgen deprivation therapy on cardiovascular disease and diabetes. J Clin Oncol 27: 3452-3458.
34. Keating NL, O'Malley J, Stephen J, Smith MR, 2010 Diabetes and cardiovascular disease during androgen deprivation therapy: observational study of veterans with prostate cancer. J Natl Cancer Inst 102: 39-46.
35. Tsai HT, Keating NL, Stephen K, et al, 2015 Risk of diabetes among patients receiving primary androgen deprivation therapy for clinically localized prostate cancer. J Urol 193: 1956-1962.
36. Keating N, Liu P, O'Malley A, Freedland S, Smith M, 2014 Androgen-deprivation therapy and diabetes control among diabetic men with prostate cancer. Eur Urol 65: 816-824.
37. Morote J, Gomez-Caamano A, Alvarez-Ossorio J, et al, 2015 The metabolic syndrome and its components in patients with prostate cancer on androgen deprivation therapy. J Urol 193: 1963-1969.
38. American Diabetes Association, 2008 Standards of medical care in diabetes–2008. Diabetes Care 31: Suppl 1: 12-54.
39. American Diabetes Association, 2009 Diagnosis and classification of diabetes mellitus. Diabetes Care 32: Suppl 1: 62-67.
40. Shahani S, Braga-Basaria M, Basaria S, 2008 Androgen deprivation therapy in prostate cancer and metabolic risk for atherosclerosis. JCEM 93: 2042-2049.
41. Braga-Basaria M, Dobs AS, Muller DC, et al, 2006 Metabolic syndrome in men with prostate cancer undergoing long-term androgen-deprivation therapy. J Clin Oncol 24: 3979-3983.
42. Prospective Study Collaboration, Lewington S, Whitlock G, Clarke R, et al, 2007 Blood cholesterol and vascular mortality by age, sex, and blood pressure: a meta-analysis of individual data from 61 prospective studies with 55,000 vascular deaths. Lancet 370: 1829-1839.
43. Rezaei MM, Rezaei MM, Ghoreifi A, Kerigh BF, 2016 Metabolic syndrome in patients with prostate cancer undergoing intermittent androgen-deprivation therapy. Can Urol Assoc J 10: 9-10.
44. Csongrádi É, Káplár M, Nagy B Jr, 2017 Adipokines as atherothrombotic risk factors in obese subjects: Associations with haemostatic markers and common carotid wall thickness. Nutr Metab Cardiovasc Dis 27: 571-580.
45. Wilt TJ, Bloomfield HE, MacDonald R, et al, 2004 Effectiveness of statin therapy in adults with coronary heart disease. Arch Intern Med 164: 1427-1436.
46. Smith MR, Malkowicz SB, Chu F, et al, 2008 Toremifene increases bone mineral density in men receiving androgen deprivation therapy for prostate cancer: interim analysis of a multicenter phase 3 clinical study. J Urol 179: 152-155.
47. Zarotsky V, Huang MY, Carman W, et al, 2014 Systematic literature review of the risk factors, comorbidities, and consequences of hypogonadism in men. Andrology 2: 819-834.
48. Smith MR, Lee H, McGovern F, et al, 2008 Metabolic changes during gonadotropin-releasing hormone agonist therapy for prostate cancer: Differences from the classic metabolic syndrome. Cancer 112: 2188-2194.
49. Davis MK, Rajala JL, Tyldesley S, Pickles T, Virani SA, 2015 The prevalence of cardiac risk factors in men with localized prostate cancer undergoing androgen-deprivation therapy in British Columbia, Canada. J Oncol 2015: 820403.
50. Alberti KG, Zimmet P, Shaw J, 2005 The metabolic syndrome: a new worldwide definition. Lancet 366: 1059-1062.

51. Samper Ots PM, Muñoz García JL, Ríos Kavadoy Y, et al, 2015 SIMBOSPROST: Prevalence of metabolic syndrome and osteoporosis in prostate cancer patients treated with radiotherapy and androgen deprivation therapy: A multicentre, cross-sectional study. Rep Pract Oncol Radiother 5: 370-376.
52. Allan CA, McLachlan RI, 2010 Androgens and obesity. Curr Opin Endocrinol Diabetes Obes 17: 224-232.
53. Munoz Garcia J, Samper Ots P, Rios Kavadoy Y, et al, 2013 Cross-section observational study about prevalence of metabolic syndrome and osteoporosis in prostate cancer treated with androgen-deprivation therapy and their impact on quality of life (SIMBOSPROST): Gicor Group. Intl J Rad Onc Bio Phys 87: Suppl: 356.
54. Valverde J, Planas Morin J, Salvador Lacambra C, et al, 2011 Prevalence of metabolic syndrome in prostatecancer patients under androgen-deprivation therapy: Interim results of a case-control study. Eur Urol Suppl 10: 337.
55. Bosco C, Bosnyak Z, Malmberg A, Adolfsson J, Keating N, Van Hemelrijck M, 2015 (2015a) Quantifying observational evidence for risk of fatal and nonfatal cardiovascular disease following androgen deprivation therapy for prostate cancer: a meta-analysis. Eur Urol 68: 386-396.
56. Beilin J, Ball EM, Favaloro JM, Zajac JD, 2000 Effect of the androgen receptor CAG repeat polymorphism on transcriptional activity: specificity in prostate and non-prostate cell lines. J Mol Endocrinol 25: 85-96.
57. Stanworth RD, Kapoor D, Channer KS, Jones TH, 2008 Androgen receptor CAG repeat polymorphism is associated with serum testosterone levels, obesity and serum leptin in men with type 2 diabetes. Eur J Endocrinol 159: 739-746.
58. Zitzmann M, Gromoll J, von Eckardstein A, Nieschlag E, 2003 The CAG repeat polymorphism in the androgen receptor gene modulates body fat mass and serum concentrations of leptin and insulin in men. Diabetologia 46: 31-39.
59. Möhlig M, Arafat AM, Osterhoff MA, et al, 2011 Androgen receptor CAG repeat length polymorphism modifies the impact of testosterone on insulin sensitivity in men. Eur J Endocrinol 164: 1013-1018.
60. Trujillo ME, Scherer PE, 2005 Adiponectin journey from an adipocyte secretory protein to biomarker of the metabolic syndrome. J Intern Med 257: 167-175.
61. Hamilton EJ, Gianatti E, Strauss BJ, et al, 2011 Increase in visceral and subcutaneous abdominal fat in men with prostate cancer treated with androgen deprivation therapy. Clin Endocrinol 3: 377-383.
62. Scailteux LM, Naudet F, Alimi Q, 2016 Mortality, cardiovascular risk, and androgen deprivation therapy for prostate cancer: A systematic review with direct and network meta-analyses of randomized controlled trials and observational studies. Medicine (Baltimore) 95: e3873.
63. Haffner SM, 2006 The metabolic syndrome: Inflammation, diabetes mellitus and cardiovascular disease. Am J Cardiol 97: 3A-11A.
64. Berruti L, Dogliotti C, Terrone, et al, 2002 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 167: 2361-2367.
65. Keating NL, O'Malley AJ, Freedland SJ, Smith MR, 2013 Does comorbidity influence the risk of myocardial infarction or diabetes during androgen-deprivation therapy for prostate cancer? Eur Urol 64: 159-166.
66. Zareba P, Duivenvoorden W, Leong DP, Pinthus JH, 2016 Androgen deprivation therapy and cardiovascular disease: what is the linking mechanism? Ther Adv Urol 8: 118-129.
67. Tsai HK, D'Amico AV, Sadetsky N, et al, 2007 Androgen deprivation therapy for localized prostate cancer and the risk of cardiovascular mortality. J Natl Cancer Inst 99: 1516-1524.
68. Efstathiou JA, Bae K, Shipley WU, et al, 2009 Cardiovascular mortality after androgen deprivation therapy for locally advanced prostate cancer: RTOG 85-31. J Clin Oncol 27: 92-99.
69. Roach III M, Bae K, Speight J, et al, 2008 Short-term neoadjuvant androgen deprivation therapy and external-beam radiotherapy for locally advanced prostate cancer: long-term results of RTOG 86-10. J Clin Oncol 26: 585-591.
70. Efstathiou JA, Bae K, Shipley WU, et al, 2008 Cardiovascular mortality and duration of androgen deprivation for locally advanced prostate cancer: analysis of RTOG 92-02. Eur Urol 54: 816-824.
71. Nguyen PL, Je Y, Schutz FA, et al, 2011 Association of androgen deprivation therapy with cardiovascular death in patients with prostate cancer: a meta-analysis of randomized trials. JAMA 306: 2359-2366.
72. Bolla M, de Reijke TM, Van Tienhoven G, et al, 2009 Duration of androgen suppression in the treatment of prostate cancer. N Engl J Med 360: 2516-2527.
73. Piccirillo JF, Tierney RM, Costas I, et al, 2004 Prognostic importance of comorbidity in a hospital-based cancer registry. JAMA 291: 2441-2447.
74. Smith MR, Klotz L, van der Meulen E, et al, 2011 Gonadotropin-releasing hormone blockers and cardiovascular disease risk: analysis of prospective clinical trials of degarelix. J Urol 186: 1835-1842.
75. Albertsen PC, Klotz L, Tombal B, et al, 2014 Cardiovascular morbidity associated with gonadotropin releasing hormone agonists and an antagonist. Eur Urol 65: 565-573.
76. Stamler J, Stamler R, Neaton JD, et al, 1999 Low risk-factor profile and long-term cardiovascular and non-cardiovascular mortality and life expectancy: findings for 5 large cohorts of young adult and middle-aged men and women. JAMA 282: 2012-2018.

77. Lim TH, Orija IB, Pearlman BL, 2014 American College of Cardiology; American College of Cardiology. The new cholesterol treatment guidelines from the American College of Cardiology/American Heart Association, 2013: what clinicians need to know. Postgrad Med 126: 35-44.
78. Wall BA, 2016 Androgen deprivation therapy and cardiovascular disease risk – The role of exercise in prostate cancer treatment. Frontiers in Oncology 6: 200.
79. Galvão DA, Taaffe DR, Spry N, 2010 Combined resistance and aerobic exercise program reverses muscle loss in men undergoing androgen suppression therapy for prostate cancer without bone metastases: a randomized controlled trial. J Clin Oncol 28: 340-347.
80. Taaffe DR, Newton RU, Spry N, 2017 Effects of different exercise modalities on fatigue in prostate cancer patients undergoing androgen deprivation therapy: A year-long randomised controlled trial. Eur Urol [Epub ahead of Print].
81. Gaskin CJ, Fraser SF, Owen PJ, Craike M, Orellana L, Livingston PM, 2016 Fitness outcomes from a randomised controlled trial of exercise training for men with prostate cancer: the ENGAGE study. J Cancer Surviv 10: 972-980.
82. Teleni L, Chan RJ, Chan A, 2016 Exercise improves quality of life in androgen deprivation therapy-treated prostate cancer: systematic review of randomised controlled trials. Endocr Relat Cancer 23: 101-112.