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Androgen Receptor Roles in Insulin Resistance and Obesity in Males: The Linkage of Androgen-Deprivation Therapy to Metabolic Syndrome

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METHODOLOGY REVIEW

Prostate cancer (PCa) is one of the most frequently diagnosed malignancies in men. Androgen-deprivation therapy (ADT) is the first-line treatment and fundamental management for men with advanced PCa to suppress functions of androgen/androgen receptor (AR) signaling. ADT is effective at improving cancer symptoms and prolonging survival. However, epidemiological and clinical studies support the notion that testosterone deficiency in men leads to the development of metabolic syndrome that increases cardiovascular disease risk. The underlying mechanisms by which androgen/AR signaling regulates metabolic homeostasis in men are complex, and in this review, we discuss molecular mechanisms mediated by AR signaling that link ADT to metabolic syndrome. Results derived from various AR knockout mouse models reveal tissue-specific AR signaling that is involved in regulation of metabolism. These data suggest that steps be taken early to manage metabolic complications associated with PCa patients receiving ADT, which could be accomplished using tissue-selective modulation of AR signaling and by treatment with insulin-sensitizing agents.

Prostate cancer (PCa) is the second leading cause of cancer-related mortality and the most common malignancy in men in the U.S. (1). Androgen-deprivation therapy (ADT) to suppress PCa was initially demonstrated by Huggins and Hodges in 1941 (2) and remains as the standard treatment for PCa (3). ADT is accomplished with surgical castration (bilateral orchiectomy) or chemical castration with gonadotropin-releasing hormone (GnRH) agonists to suppress binding of androgen to the androgen receptor (AR). Although ADT improves survival at all stages of PCa, it leads to severe hypogonadism with different adverse effects, including unfavorable metabolic alterations. Treatment of the metabolic complications of ADT has been considered and has become increasingly important (4). Metabolic syndrome is a complex disorder consisting of abdominal obesity, dyslipidemia, insulin resistance, and hypertension. Obese individuals are more prone to develop insulin resistance compared with nonobese individuals. Insulin resistance promotes metabolic complications including elevated circulating triglycerides, reduced HDL, elevated fasting blood glucose levels, and high blood pressure. These metabolic abnormalities, in conjunction with abdominal obesity, represent the classical features of metabolic syndrome (5). Metabolic syndrome is an important risk factor for cardiovascular disease and associated morbidity and mortality in individuals with or without diabetes.

In this article, we will discuss the molecular aspects of mechanisms linking ADT to metabolic syndrome by focusing on evidence derived from AR-knockout (ARKO) mouse models.

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RELATIONSHIP BETWEEN ANDROGEN DEFICIENCY AND METABOLIC SYNDROME: EVIDENCE FROM EPIDEMIOLOGICAL AND CLINICAL STUDIES

Androgen is a male sex steroid hormone that exerts important physiological functions leading to masculine characteristics, maturation of reproductive systems, and bone metabolism. The major circulating androgen, testosterone, is synthesized in testicular Leydig cells and released into blood, where it binds to steroid hormone-binding globulin (SHBG) to facilitate the transport. Within target cells, testosterone is converted to 5α-dihydrotestosterone (DHT), a more potent androgen, by 5α-reductase. Both testosterone and DHT bind to the AR to exert their physiological functions (6). Androgen-activated AR regulates the transcription of a variety of target genes through the interaction with different coregulators. Androgen/AR and their coregulators form a complex signaling network.

Androgen is an important determinant of body composition in men promoting growth of lean mass and suppressing deposition of fat (7). Epidemiological studies have observed a bidirectional relationship between low testosterone levels and obesity in men (8). Obesity is the single most powerful predictor of low testosterone levels in men, and one of the hallmarks of obesity in men is reduced testosterone levels. Conversely, low levels of testosterone and SHBG can predict accumulation of intra-abdominal fat, development of central obesity, and increased risk of metabolic syndrome in men (8,9).

There is growing evidence supporting a beneficial effect of testosterone therapy on body composition to reduce visceral obesity and the elements of metabolic syndrome (10,11). Results from clinical studies show that testosterone can promote insulin sensitivity in hypogonadal men with and without diabetes (12). Testosterone replacement in men with metabolic syndrome reduces body weight, waist circumference, and visceral fat mass. Plasma levels of insulin and leptin as well as some markers of inflammation were also reduced (13). Testosterone replacement therapy may also have the potential to decrease risk factors of cardiovascular diseases associated with metabolic syndrome in hypogonadal men (14).

High body-fat mass and central obesity are associated with low serum testosterone and SHBG levels (15). Reduction of testosterone levels in men with BMI $\geq$30 kg/m^2 was demonstrated in the European Male Aging study, suggesting that obesity can lead to decreased testosterone levels (16). This is further supported by studies showing that weight management by diet or surgery can increase testosterone levels proportional to the amount of weight lost (17,18). In contrast, abnormalities in the hypothalamo-pituitary-testicular axis or experimental induction of hypogonadism in healthy young men can increase fat mass rapidly (8,19).

Low testosterone and SHBG are also associated with the development of insulin resistance and metabolic syndrome in men. Cross-sectional studies have shown an inverse relationship between testosterone levels and insulin resistance in healthy men (20). In aging men, a 25% decrease of serum testosterone leads to a twofold increase of insulin resistance (21). Acute androgen deprivation can reduce insulin sensitivity in healthy young men (22). Moreover, reduction in the total and free serum testosterone is prevalent in men with type 2 diabetes (23). These results support the notion that male hypogonadism is an independent risk factor for metabolic syndrome, and low testosterone levels can be added to the criteria for the diagnosis of metabolic syndrome in men (24).

Taken together, results derived from epidemiological and clinical studies reveal a close association between testosterone deficiency and metabolic syndrome. Given that ADT induces severe testosterone deficiency with a temporally defined onset, PCa patients receiving ADT may have even higher risks for development of metabolic syndrome as well as detrimental changes in body composition associated with the ADT treatment, for example, an increase in fat mass and a decrease in lean mass (25–27). Three months of ADT treatment significantly increases fat mass and circulating insulin levels (27). The accumulation of visceral adiposity during short-term ADT is highly correlated with increasing circulating insulin levels. Interestingly, changes in measures of insulin resistance are noted as early as 3 months after starting ADT even before the development of central obesity (28). Men undergoing long-term ADT treatment show significant insulin resistance and hyperglycemia compared with the non-ADT and control groups (29,30). Importantly, 44% of patients receiving ADT have a fasting glucose level $>$126 mg/dL, a criterion for the diagnosis of diabetes mellitus, indicating that ADT of long duration can lead to development of diabetes (31).

In addition to the linkage of low testosterone levels with metabolic disturbances, the CAG repeat polymorphism within the AR gene also can play a role in development of metabolic syndrome. There is an inverse relationship between the length of the AR CAG repeat and its transcriptional activity on testosterone target genes (32). Some studies even suggest that serum levels of testosterone can be correlated with the CAG repeat of AR, indicating the negative-feedback loop mediated by AR to regulate testosterone levels (33). The polymorphism of AR CAG repeats is reported to influence insulin sensitivity and components of metabolic syndrome in men (34,35). These findings provide additional support for the critical role of AR in androgen/AR signaling in the regulation of metabolism.

LESSONS FROM GLOBAL ARKO MOUSE MODEL

Although human studies have linked testosterone deficiency to the metabolic complications that occur in men receiving ADT, studying the underlying mechanisms responsible in vivo is complex. The mechanisms by which testosterone influences insulin sensitivity and obesity are multifactorial and are likely due to a combination of

testosterone's action on liver, muscle, and adipose tissues. The molecular basis of functional deficiency in androgen/AR signaling and the pathophysiology of developing obesity and insulin resistance remain unclear. Using the Cre-loxP–mediated recombination approach, a conditional ARKO mouse model was established to investigate roles of AR in the development of metabolic syndrome in males (36).

Global deletion of AR (GARKO) in male mice results in the characteristics of central obesity, abdominal accumulation of fat by middle age, but without change in lean mass (37). The development of late-onset visceral obesity is also observed in several parallel studies using mouse models with genetic AR deletion (38–40). Obesity in male GARKO mice was associated with elevations of circulating lipids, altered lipid metabolism in white adipose tissue, and excessive deposition of lipids in nonadipose tissues, including liver and muscle. Glucose homeostasis was affected in male GARKO mice that demonstrate fasting hyperglycemia, glucose intolerance, and insulin resistance. The ability of insulin to stimulate activation of downstream phosphatidylinositide-3 kinase was reduced by 60–63% in skeletal muscle and liver derived from male GARKO mice, supporting the development of insulin resistance and impaired insulin signaling. Leptin resistance in these obese male GARKO mice was also demonstrated by the reduced response of mice to exogenous leptin in regulation of food intake and body weight (37).

Circulating testosterone levels were remarkably low in GARKO male mice due to atrophic testes, suggesting the possibility that the insulin resistance and observed metabolic abnormalities simply reflected low levels of serum testosterone. Interestingly, serum androstenedione and estradiol were not altered in male ARKO mice and their wild-type littermates. When the nonaromatizable androgen DHT was given to male GARKO mice, DHT was not able to reverse the metabolic abnormalities and insulin resistance (37). These findings indicate that nongenomic actions of androgen cannot directly account for the development of obesity and insulin resistance (41) and that AR is critical in mediating effects of androgens to regulate glucose and lipid metabolism.

Although compensatory mechanisms caused by congenital ablation of AR could occur and influence metabolism in the adult, the metabolic abnormalities developed in male GARKO mice in fact recapitulated the metabolic complications observed in men with testosterone deficiency and in patients with PCa receiving ADT. The ARKO mouse model therefore may serve as an in vivo system to investigate molecular mechanisms by which androgen/AR signaling regulate glucose and lipid homeostasis.

CELL TYPE–SPECIFIC ARKO MOUSE MODELS

The development of insulin resistance is a complicated process involving the impaired action of insulin in various target tissues. Although underlying mechanisms of impaired insulin signaling may differ among tissues and under various circumstances, it is established that there are complex interorgan communication among various insulin target tissues (42,43). Examination of tissue-specific insulin signaling and selective insulin resistance in various tissues have advanced our understanding of the complex pathophysiology of insulin action (44).

By using transgenic mice expressing Cre recombinase in specific cell types, tissue-specific ARKO mouse models have been generated (37,45–47). Deletion of AR in this manner does not alter the serum testosterone levels in male mice (Table 1). These various ARKO mice serve as valuable animal models to dissect the pathophysiological roles of tissue-specific AR signaling involved in the development of metabolic syndrome.

Table 1—Summary of metabolic phenotypes in male conditional ARKO mice

Conditional ARKO mice	GARKO ($AR^{-/y}$)	LARKO (L-$AR^{-/y}$)	AARKO (A-$AR^{-/y}$)	NARKO (N-$AR^{-/y}$)
Cell specificity	General	Hepatocytes	Adipocytes	Neurons
Cre promoter	β-actin	Albumin	FABP4	Synapsin I
Insulin sensitivity	↓	↓	↔	↓
Serum insulin	↑	↑	↔	↑
Blood glucose	↑	↑	↔	↑
Glucose tolerance	↓	↓	ND	↓
Leptin sensitivity	↓	ND	↑	ND
Serum leptin	↑	↑	↑	↑
Hepatic lipids	↑	↑	↓	↑
Serum triglycerides	↑	↑	↓	↑
Free fatty acids	↑	↔	↔	↑
Visceral fat accumulation	↑	↑	↔	↑
Serum testosterone level	↓	↔	↔	↔

NARKO, neuronal-specific ARKO; ND, not determined.

Liver-Specific ARKO Mouse Model

The liver functions as a major metabolic tissue to control glucose and lipid homeostasis. Oxidation of fatty acids by the hepatocytes supplies the substrate for glucose production. Dysregulated fatty acid oxidation and synthesis can lead to the accumulation of fat or hepatic steatosis.

Using albumin-Cre–transgenic mice, Lin et al. (45) directly addressed the role of AR in the liver by specifically deleting AR in hepatocytes (LARKO). After 8 weeks of high-fat diet (HFD) feeding, male LARKO mice developed obesity and significant hepatic steatosis (45). Hepatic steatosis is known to negatively impact insulin sensitivity and lead to insulin resistance, which is manifested by the reduced ability of insulin to suppress hepatic glucose production (48,49). HFD-fed male LARKO mice exhibited fasting hyperglycemia and insulin resistance, indicating impairments in the regulation of glucose homeostasis and insulin sensitivity. At a molecular level, decreased activation of phosphatidylinositide-3 kinase in response to insulin and increased expression of PEPCK in male LARKO liver and isolated hepatocytes were consistent with increased hepatic glucose production and development of insulin resistance.

Mechanistic studies in male LARKO mice showed that activation and upregulation of SREBP1c and acetyl CoA carboxylase produced more malonyl CoA, the substrate for de novo fatty acid synthesis. The transport of free fatty acids from the cytosol to mitochondria is required for their β-oxidation and is mediated by carnitine palmitoyltransferase I, located at the outer membrane of mitochondria. Malonyl CoA is an inhibitor of carnitine palmitoyltransferase I, and increased levels of malonyl CoA reduces transport of fatty acids into mitochondria, resulting in the reduction of fatty-acid oxidation. In a parallel cascade, reduction of peroxisome proliferator–activated receptor-α and malonyl CoA decarboxylase in livers derived from male LARKO mice further increased the production of malonyl CoA. In corresponding hepatocytes, expression of peroxisome proliferator–activated receptor-α was shown to be mediated by DHT-dependent activation of AR (45). These findings suggest that impeding the entry of free fatty acids into mitochondria, impairing β-oxidation of fatty acids, and promotion of de novo fatty acid synthesis could account for the development of hepatic steatosis in male LARKO mice.

These mechanistic studies of HFD-fed male LARKO mice demonstrate a pivotal role of hepatic AR in regulating insulin sensitivity and lipid homeostasis. Hepatic insulin resistance is shown to be sufficient to produce dyslipidemia and increase the susceptibility to atherosclerosis in mice (50,51). In human clinical studies, GnRH agonists to suppress androgen/AR signaling cause increases in total cholesterol and triglycerides (52,53). It is therefore likely that functional deficiency of AR in the liver caused by GnRH agonists leads to these lipid alterations. As large cohort studies demonstrate strong correlations between blood cholesterol levels and cardiovascular mortality independent of other coronary risk factors (54), awareness of altered hepatic AR signaling and lipid metabolism during ADT should prompt the appropriate management of cardiovascular complications.

Neuronal-Specific ARKO Mouse Model

Compelling data derived from animal studies are mounting that brain insulin resistance may be a critical element in the pathophysiology of obesity, type 2 diabetes, and related metabolic disorders (55–57). Defective hypothalamic insulin signaling is able to promote hepatic insulin resistance as demonstrated by the brain-specific insulin receptor knockout mouse model (55). Partial restoration of liver insulin signaling in the insulin receptor knockout mice fails to normalize insulin action on hepatic glucose production, supporting the importance of hypothalamic insulin signaling in glucose homeostasis (58).

Male neuronal-specific ARKO mice, generated by selectively targeting AR in neurons, displayed increased body weight and visceral adiposity, as well as increased levels of fasting blood glucose and insulin. Neuronal AR deficiency led to impaired insulin signaling in the hypothalamus, which in turn resulted in reduced suppression of hepatic gluconeogenic genes (46).

Hypothalamic insulin resistance is reported to act as an early event in the development of systemic insulin resistance due to prolonged exposure to excessive nutrition (59). Activation of hypothalamic nuclear factor-κB (NF-κB) signaling is critical to induction of insulin resistance following chronic overnutrition (60,61) At the neuronal level, loss of suppression by AR resulted in increased activation of hypothalamic NF-κB signaling within a short-term HFD-feeding period (46). Hence, functional deficiency of AR in neurons directly interferes with insulin signaling and leads to hypothalamic insulin resistance.

These findings uncover a new mechanism of insulin resistance caused by testosterone deficiency through decreased function of AR in the brain. Suppression of the hypothalamic NF-κB by AR provides a potential way to manage the metabolic complications that develop in patients with PCa undergoing ADT by targeting neuronal AR.

Adipose-Specific ARKO Mouse Model

The adipose tissue is a key target of insulin action, important for glucose uptake, and a potential site for testosterone's action in regulating body mass composition.

Selectively targeting AR in adipocytes was used to generate the adipose-specific ARKO (AARKO) mouse model to study the role of AR in fat tissue. In male AARKO mice, body weight and fat pad mass were indistinguishable from that of wild-type littermates. Despite identical levels of adiposity, male AARKO mice exhibited elevated levels of serum leptin, suggesting that loss of the AR affects leptin secretion by adipose tissue. Interestingly, enhanced leptin production in AR-deficient adipose tissue did not result in leptin resistance, as male

AARKO mice showed increased sensitivity in response to exogenous leptin challenge (47). Increased estradiol levels were observed in epididymal adipose tissue, suggesting enhanced estrogen receptor (ER) transactivation contributed to upregulation of leptin gene transcription.

Adipose tissue expressed several steroidogenic enzymes that control tissue steroid concentrations and ligand bioavailability for intracellular receptors (62). It is possible that altered activities of steroid-converting enzymes due to loss of AR resulted in a larger steroid reservoir in AR-deficient adipocytes. Increased steroid precursors may have provided increased available substrate for aromatases in the adipose tissue, resulting in enhanced estradiol production. In male GARKO mice, the elevation of leptin occurred prior to the onset of obesity, suggesting a similar mechanism of increased intracellular estradiol conversion may have contributed to enhanced leptin production (37).

Sex steroid hormones are important regulators of metabolism, accumulation of fat, and distribution of adipose tissue. In humans, fat distribution is different between males and females. Sex steroid hormones predispose males to a more central accumulation of fat, whereas in females, a more subcutaneous accumulation of fat is observed (63). This difference has important metabolic consequences, as visceral obesity is considered a risk factor for cardiovascular diseases, and men have a higher incidence of cardiovascular diseases than women. Menopause in women increases central distribution of fat and incidence of cardiovascular diseases (64). The mechanism by which sex steroid hormones control the amount and distribution of fat is not clear. One mechanism may be through the transcriptional regulation of key proteins in adipose tissue (63). Future studies on the local synthesis of sex steroid hormones and the regulation of AR and ER signaling in different types of adipose tissue may increase our understanding of steroid action in the adipocyte.

Muscle-Specific ARKO Mouse Model

A critical feature of skeletal muscle in glucose homeostasis is insulin-stimulated glucose uptake and use. Testosterone is an important regulator of lean mass, and anabolic effects of testosterone on skeletal muscles are thought to be mediated predominantly through AR. AR is expressed in various cell types of skeletal muscle in humans and rodents including myocytes, satellite cells, fibroblasts, and mesenchymal stem cells (65–67), and all are potential targets of testosterone's action.

One muscle-specific ARKO (MARKO) mouse model, generated by myocyte-specific AR deletion, demonstrates altered fiber composition. Myocyte-specific deletion of AR resulted in an increase of slow-twitch fibers without affecting muscle strength. Unexpectedly, MARKO mice showed a reduction in intra-abdominal fat mass (68). In another MARKO mouse model, AR ablation in myocytes affected intrinsic contractile functions in fast- and intermediary-twitch muscles. Androgens induced hypertrophy of muscle fibers through AR-dependent pathways in perineal muscles and AR-independent pathways in limb muscles (69). Discrepancies between the two MARKO mouse models may be related to differences in genetic backgrounds of the mouse lines, Cre recombinase transgenic mouse lines (MCK-Cre vs. HSA-Cre), and experimental protocols used. Whether insulin sensitivity or glucose homeostasis is influenced by myocyte-specific AR ablation is unclear and awaits further investigation.

Insights into AR signaling in muscle and the role of AR in regulating metabolic homeostasis may be facilitated by using transgenic animal models in which AR is selectively overexpressed in various cell types. Overexpression of AR in myoctes increased lean mass and reduced fat mass in transgenic rats. AR signaling in myocytes was sufficient to promote systemic oxidative metabolism through increasing activity of mitochondrial enzymes and oxygen consumption in skeletal muscle (70). Targeted AR overexpression in mesenchymal stem cells reduced fat mass and reciprocally increased lean mass in male mice. Transgenic AR mice showed improved glucose use in response to exogenous glucose challenge (71). These studies suggest AR signaling in muscle is involved in mitochondrial respiration and glucose disposal.

ROLES OF ANDROGEN AND AR IN METABOLIC SYNDROME–ASSOCIATED CARDIOVASCULAR DISEASE

Metabolic syndrome is a critical risk factor for cardiovascular disease. The metabolic complications associated with ADT suggest a significantly greater risk of cardiovascular disease events in patients with PCa, although the role of androgen in cardiovascular disease is controversial. Epidemiologic studies indicate that men are at a significantly higher risk of cardiovascular disease and suffer from mortality more frequently compared with women (72,73). Exogenous testosterone administration in men increases the rate of adverse cardiovascular events, including the coronary syndrome and myocardial infarction (74). The risk of developing deep venous thrombosis or pulmonary embolism in men receiving testosterone-replacement therapy has also been suggested in a recent study (75). In contrast, other clinical studies suggest a beneficial action of testosterone on vascular health and low levels of testosterone are associated with risk of cardiovascular disease (76,77). Low testosterone levels are associated with carotid and aortic atherosclerosis in men (78,79) and are a predictor of cardiovascular events in middle-aged men after adjustment for coronary risk factors (80). In men with coronary artery disease, low levels of testosterone are associated with severity of the coronary artery atherosclerosis (81). Thus, there is evidence that high levels of testosterone as well as low levels of testosterone are associated with increased cardiovascular disease risk.

Controversies are also observed in cell culture and animal studies designed to uncover actions of testosterone on the cardiovascular system. Deleterious effects of

testosterone on vasoconstriction and inflammation were shown to contribute to the progression of atherosclerosis and rupture of the myocardium following acute myocardial infarction (82–87). In contrast, much of the literature shows that testosterone can attenuate atherosclerosis, reduce the size of the myocardial infarction, and enhance vasodilation, suggesting a beneficial role of testosterone (88–93). This paradox suggests that testosterone may execute multiple roles on the cardiovascular system simultaneously in addition to its effects on risk factors, such as insulin sensitivity, dyslipidemia, obesity, and diabetes.

Although some effects of testosterone on the cardiovascular system are thought to be mediated by the ER, AR is present in all types of cells within the cardiovascular system (94). AR is expressed in endothelial cells, smooth muscle cells, macrophages, platelets, and cardiomyocytes (95,96). Testosterone itself results in a 50% increase of AR expression in the aortic arterial segment of rabbits. The vascular AR is suggested to be involved in the process of testosterone's action on the arterial vascular system (97). Osterlund et al. (98) has demonstrated AR-mediated inflammatory responses in isolated coronary artery smooth muscle cells. Furthermore, AR was shown to regulate cell proliferation in cardiomyocytes and mediate protective effects of testosterone in response to ischemic insults in rats (91,99). These studies suggest direct AR-mediated action of androgen in the cardiovascular system. It is therefore likely that AR acts in either a beneficial or harmful manner for vascular health in different cell types within the microenvironment.

Although controversial roles of androgen/AR signaling exist in the cardiovascular system, several clinical studies have reported adverse cardiovascular consequences of ADT in patients with PCa. Men who receive a GnRH agonist had a higher incidence of coronary heart disease, myocardial infarction, and sudden cardiac death (31). The use of ADT was associated with shorter time to death from cardiovascular causes and to fatal myocardial infarction after controlling for age and risk factors (100,101). In a retrospective observational study, the overall survival at 10 years was worse in men receiving ADT treatment, and cardiovascular disease was the most common cause of death in these cases (102).

The underlying mechanisms through which severe deficiency of androgen/AR signaling in ADT results in rapid development of cardiovascular disease complications remain largely unknown. Besides enhancing the development of components of metabolic syndrome, such as insulin resistance, dyslipidemia, and visceral obesity, deficiency of androgen/AR signaling may also directly impact health of the cardiovascular system. We suggest that specifically targeting AR in various cell types in the cardiovascular system may help to reveal the complex relationship between androgen and cardiovascular disease. These future investigations will shed light on better management of long-term cardiovascular health for patients with PCa receiving ADT.

SUMMARY

A growing body of evidence in human studies demonstrates a close relationship between testosterone deficiency and the development of metabolic syndrome in men. In this review, we discussed several molecular mechanisms mediated by AR signaling that can lead to the development of metabolic syndrome. In patients with PCa receiving ADT, severe testosterone deficiency results in obesity, insulin resistance, altered lipid profiles, development of diabetes, and cardiovascular complications. However, the molecular mechanisms by which androgen/AR signaling regulates metabolic homeostasis in men are likely to involve multiple factors and cross-talk among insulin target tissues. By cell type–specific AR targeting in mice, the critical role of AR in androgen/AR signaling can be studied without alterations of testosterone levels in male mice. Results derived from various cell type–specific ARKO mouse models for the tissue-specific AR signaling are summarized in Table 1. Hepatic AR and neuronal AR signaling directly participate in cellular insulin signaling regulating systemic insulin sensitivity as well as glucose and lipid homeostasis. Awareness of altered hepatic AR signaling and lipid metabolism may prompt appropriate management of cardiovascular complications during ADT. AR signaling in the myocytes beneficially increases systemic oxidative metabolism by changing muscle fiber compositions in skeletal muscle. These findings suggest promising targets for tissue-selective treatments to manage metabolic complications found in patients with PCa during ADT.

FUTURE PROSPECTS

In the future, rather than waiting for the diagnosis of insulin resistance and metabolic syndrome, available data suggest that patients with PCa receiving ADT should be given advice on lifestyle modification and possible early treatment for ensuing lipid disorders leading to metabolic syndrome.

The selective AR modulators (SARMs), a class of ligands that bind to the AR and display a tissue-selective activation of AR signaling, may provide a treatment choice (103). In preclinical studies, a SARM was shown to execute tissue-selective anabolic actions by restoring muscle strength and reducing body fat in ovariectomized male rats (104,105). In phase I clinical studies, first-generation SARMs induced modest gain of lean body mass in healthy volunteers (106). With improving techniques, the new generation of SARM molecules will have greater potency and better selectivity. One new SARM molecule has shown to improve lean body mass and physical function in healthy elderly men in a phase II trial study (107). The use of nonsteroidal SARMs may avoid differential activation of intracellular signaling cascades by the nongenomic action of DHT that can lead to unexpected cellular processes (106,108).

Obesity and diabetes are being recognized as risk factors for the development of cancers and prediction of aggressive cancer metastasis, including PCa. A pilot study

has shown a strong trend between metabolic syndrome and earlier development of castration-resistant PCa in patients receiving ADT (109). These findings suggest that there may be a unique therapeutic window for combining insulin-sensitizing medication with antiandrogen agents for treatment of patients with PCa affected by metabolic syndrome and advanced PCa (110,111).

It is anticipated that patients with PCa will live longer with next-generation therapies targeting androgen synthesis or directly targeting AR in combination with ADT and with better management of metabolic and cardiovascular risk factors and complications. The development of cell type–specific AR targeting or functional AR restoration is clearly warranted in the future.

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References

1. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2012. CA Cancer J Clin 2012;62:10–29

2. Huggins C, Hodges CV. Studies on prostatic cancer. I. The effect of castration, of estrogen and of androgen injection on serum phosphatases in metastatic carcinoma of the prostate. 1941. J Urol 2002;167:948–951; discussion 952

3. Hodges CV, Lehman TH, MacFarlane CA. Early prostatic carcinoma; a study of causes of delay in performing surgery. J Am Med Assoc 1957;165:1905–1907

4. Faris JE, Smith MR. Metabolic sequelae associated with androgen deprivation therapy for prostate cancer. Curr Opin Endocrinol Diabetes Obes 2010;17:240–246

5. Alberti KG, Zimmet P, Shaw J; IDF Epidemiology Task Force Consensus Group. The metabolic syndrome—a new worldwide definition. Lancet 2005;366:1059–1062

6. Chang CS, Kokontis J, Liao ST. Molecular cloning of human and rat complementary DNA encoding androgen receptors. Science 1988;240:324–326

7. Vermeulen A, Goemaere S, Kaufman JM. Testosterone, body composition and aging. J Endocrinol Invest 1999;22(Suppl.):110–116

8. Allan CA, McLachlan RI. Androgens and obesity. Curr Opin Endocrinol Diabetes Obes 2010;17:224–232

9. Brand JS, van der Tweel I, Grobbee DE, Emmelot-Vonk MH, van der Schouw YT. Testosterone, sex hormone-binding globulin and the metabolic syndrome: a systematic review and meta-analysis of observational studies. Int J Epidemiol 2011;40:189–207

10. La Vignera S, Calogero AE, D'Agata R, et al. Testosterone therapy improves the clinical response to conventional treatment for male patients with metabolic syndrome associated to late onset hypogonadism. Minerva Endocrinol 2008;33:159–167

11. Saad F, Gooren LJ, Haider A, Yassin A. A dose-response study of testosterone on sexual dysfunction and features of the metabolic syndrome using testosterone gel and parenteral testosterone undecanoate. J Androl 2008;29:102–105

12. Wang C, Jackson G, Jones TH, et al. Low testosterone associated with obesity and the metabolic syndrome contributes to sexual dysfunction and cardiovascular disease risk in men with type 2 diabetes. Diabetes Care 2011;34:1669–1675

13. Kalinchenko SY, Tishova YA, Mskhalaya GJ, Gooren LJ, Giltay EJ, Saad F. Effects of testosterone supplementation on markers of the metabolic syndrome and inflammation in hypogonadal men with the metabolic syndrome: the double-blinded placebo-controlled Moscow study. Clin Endocrinol (Oxf) 2010;73:602–612

14. Saad F. Androgen therapy in men with testosterone deficiency: can testosterone reduce the risk of cardiovascular disease? Diabetes Metab Res Rev 2012;28(Suppl. 2):52–59

15. MacDonald AA, Herbison GP, Showell M, Farquhar CM. The impact of body mass index on semen parameters and reproductive hormones in human males: a systematic review with meta-analysis. Hum Reprod Update 2010;16:293–311

16. Wu FC, Tajar A, Pye SR, et al.; European Male Aging Study Group. Hypothalamic-pituitary-testicular axis disruptions in older men are differentially linked to age and modifiable risk factors: the European Male Aging Study. J Clin Endocrinol Metab 2008;93:2737–2745

17. Camacho EM, Huhtaniemi IT, O'Neill TW, et al.; EMAS Group. Age-associated changes in hypothalamic-pituitary-testicular function in middle-aged and older men are modified by weight change and lifestyle factors: longitudinal results from the European Male Ageing Study. Eur J Endocrinol 2013;168:445–455

18. Fui MN, Dupuis P, Grossmann M. Lowered testosterone in male obesity: mechanisms, morbidity and management. Asian J Androl 2014;16:223–231

19. Mauras N, Hayes V, Welch S, et al. Testosterone deficiency in young men: marked alterations in whole body protein kinetics, strength, and adiposity. J Clin Endocrinol Metab 1998;83:1886–1892

20. Simon D, Preziosi P, Barrett-Connor E, et al. Interrelation between plasma testosterone and plasma insulin in healthy adult men: the Telecom Study. Diabetologia 1992;35:173–177

21. Kupelian V, Hayes FJ, Link CL, Rosen R, McKinlay JB. Inverse association of testosterone and the metabolic syndrome in men is consistent across race and ethnic groups. J Clin Endocrinol Metab 2008;93:3403–3410

22. Yialamas MA, Dwyer AA, Hanley E, Lee H, Pitteloud N, Hayes FJ. Acute sex steroid withdrawal reduces insulin sensitivity in healthy men with idiopathic hypogonadotropic hypogonadism. J Clin Endocrinol Metab 2007;92:4254–4259

23. Stanworth RD, Jones TH. Testosterone in obesity, metabolic syndrome and type 2 diabetes. Front Horm Res 2009;37:74–90

24. Laaksonen DE, Niskanen L, Punnonen K, et al. Testosterone and sex hormone-binding globulin predict the metabolic syndrome and diabetes in middle-aged men. Diabetes Care 2004;27:1036–1041

25. Berruti A, Dogliotti L, Terrone C, et al.; Gruppo Onco Urologico Piemontese (G.O.U.P.), Rete Oncologica Piemontese. Changes in bone mineral density, lean body mass and fat content as measured by dual energy x-ray absorptiometry in patients with prostate cancer without apparent bone metastases given androgen deprivation therapy. J Urol 2002;167:2361–2367; discussion 2367

26. Smith MR, Finkelstein JS, McGovern FJ, et al. Changes in body composition during androgen deprivation therapy for prostate cancer. J Clin Endocrinol Metab 2002;87:599–603

27. Smith JC, Bennett S, Evans LM, et al. The effects of induced hypogonadism on arterial stiffness, body composition, and metabolic parameters in males with prostate cancer. J Clin Endocrinol Metab 2001;86:4261–4267

28. Harrington JM, Schwenke DC, Epstein DR, Bailey DE Jr. Androgen-deprivation therapy and metabolic syndrome in men with prostate cancer. Oncol Nurs Forum 2014;41:21–29

29. Basaria S, Muller DC, Carducci MA, Egan J, Dobs AS. Hyperglycemia and insulin resistance in men with prostate carcinoma who receive androgen-deprivation therapy. Cancer 2006;106:581–588

30. Saylor PJ, Smith MR. Metabolic complications of androgen deprivation therapy for prostate cancer. J Urol 2009;181:1998-2006; discussion 2007
31. Keating NL, O'Malley AJ, Smith MR. Diabetes and cardiovascular disease during androgen deprivation therapy for prostate cancer. J Clin Oncol 2006;24:4448–4456
32. Beilin J, Ball EM, Favaloro JM, Zajac JD. Effect of the androgen receptor CAG repeat polymorphism on transcriptional activity: specificity in prostate and non-prostate cell lines. J Mol Endocrinol 2000;25:85–96
33. Stanworth RD, Kapoor D, Channer KS, Jones TH. Androgen receptor CAG repeat polymorphism is associated with serum testosterone levels, obesity and serum leptin in men with type 2 diabetes. Eur J Endocrinol 2008;159:739–746
34. Zitzmann M, Gromoll J, von Eckardstein A, Nieschlag E. The CAG repeat polymorphism in the androgen receptor gene modulates body fat mass and serum concentrations of leptin and insulin in men. Diabetologia 2003;46:31–39
35. Möhlig M, Arafat AM, Osterhoff MA, et al. Androgen receptor CAG repeat length polymorphism modifies the impact of testosterone on insulin sensitivity in men. Eur J Endocrinol 2011;164:1013–1018
36. Yeh S, Tsai MY, Xu Q, et al. Generation and characterization of androgen receptor knockout (ARKO) mice: an in vivo model for the study of androgen functions in selective tissues [published correction appears in Proc Natl Acad Sci U S A 2002;99:15245]. Proc Natl Acad Sci U S A 2002;99:13498–13503
37. Lin HY, Xu Q, Yeh S, Wang RS, Sparks JD, Chang C. Insulin and leptin resistance with hyperleptinemia in mice lacking androgen receptor. Diabetes 2005;54:1717–1725
38. Matsumoto T, Takeyama K, Sato T, Kato S. Androgen receptor functions from reverse genetic models. J Steroid Biochem Mol Biol 2003;85:95–99
39. Sato T, Matsumoto T, Yamada T, Watanabe T, Kawano H, Kato S. Late onset of obesity in male androgen receptor-deficient (AR KO) mice. Biochem Biophys Res Commun 2003;300:167–171
40. Fan W, Yanase T, Nomura M, et al. Androgen receptor null male mice develop late-onset obesity caused by decreased energy expenditure and lipolytic activity but show normal insulin sensitivity with high adiponectin secretion. Diabetes 2005;54:1000–1008
41. Foradori CD, Weiser MJ, Handa RJ. Non-genomic actions of androgens. Front Neuroendocrinol 2008;29:169–181
42. Accili D. Lilly lecture 2003: the struggle for mastery in insulin action: from triumvirate to republic. Diabetes 2004;53:1633–1642
43. Okamoto H, Nakae J, Kitamura T, Park BC, Dragatsis I, Accili D. Transgenic rescue of insulin receptor-deficient mice. J Clin Invest 2004;114:214–223
44. Rask-Madsen C, Kahn CR. Tissue-specific insulin signaling, metabolic syndrome, and cardiovascular disease. Arterioscler Thromb Vasc Biol 2012;32:2052–2059
45. Lin HY, Yu IC, Wang RS, et al. Increased hepatic steatosis and insulin resistance in mice lacking hepatic androgen receptor. Hepatology 2008;47:1924–1935
46. Yu IC, Lin HY, Liu NC, et al. Neuronal androgen receptor regulates insulin sensitivity via suppression of hypothalamic NF-κB-mediated PTP1B expression. Diabetes 2013;62:411–423
47. Yu IC, Lin HY, Liu NC, et al. Hyperleptinemia without obesity in male mice lacking androgen receptor in adipose tissue. Endocrinology 2008;149:2361–2368
48. Samuel VT, Liu ZX, Qu X, et al. Mechanism of hepatic insulin resistance in non-alcoholic fatty liver disease. J Biol Chem 2004;279:32345–32353
49. Wang J, Obici S, Morgan K, Barzilai N, Feng Z, Rossetti L. Overfeeding rapidly induces leptin and insulin resistance. Diabetes 2001;50:2786–2791
50. Biddinger SB, Haas JT, Yu BB, et al. Hepatic insulin resistance directly promotes formation of cholesterol gallstones. Nat Med 2008;14:778–782
51. Biddinger SB, Hernandez-Ono A, Rask-Madsen C, et al. Hepatic insulin resistance is sufficient to produce dyslipidemia and susceptibility to atherosclerosis. Cell Metab 2008;7:125–134
52. Dockery F, Bulpitt CJ, Agarwal S, Donaldson M, Rajkumar C. Testosterone suppression in men with prostate cancer leads to an increase in arterial stiffness and hyperinsulinaemia. Clin Sci (Lond) 2003;104:195–201
53. Eri LM, Urdal P, Bechensteen AG. Effects of the luteinizing hormone-releasing hormone agonist leuprolide on lipoproteins, fibrinogen and plasminogen activator inhibitor in patients with benign prostatic hyperplasia. J Urol 1995;154:100–104
54. Lewington S, Whitlock G, Clarke R, et al.; Prospective Studies Collaboration. 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 2007;370:1829–1839
55. Brüning JC, Gautam D, Burks DJ, et al. Role of brain insulin receptor in control of body weight and reproduction. Science 2000;289:2122–2125
56. Gelling RW, Morton GJ, Morrison CD, et al. Insulin action in the brain contributes to glucose lowering during insulin treatment of diabetes. Cell Metab 2006;3:67–73
57. Obici S, Feng Z, Karkanias G, Baskin DG, Rossetti L. Decreasing hypothalamic insulin receptors causes hyperphagia and insulin resistance in rats. Nat Neurosci 2002;5:566–572
58. Okamoto H, Obici S, Accili D, Rossetti L. Restoration of liver insulin signaling in Insr knockout mice fails to normalize hepatic insulin action. J Clin Invest 2005;115:1314–1322
59. Ono H, Pocai A, Wang Y, et al. Activation of hypothalamic S6 kinase mediates diet-induced hepatic insulin resistance in rats. J Clin Invest 2008;118:2959–2968
60. Milanski M, Degasperi G, Coope A, et al. Saturated fatty acids produce an inflammatory response predominantly through the activation of TLR4 signaling in hypothalamus: implications for the pathogenesis of obesity. J Neurosci 2009;29:35–370
61. Zhang X, Zhang G, Zhang H, Karin M, Bai H, Cai D. Hypothalamic IKKbeta/NF-kappaB and ER stress link overnutrition to energy imbalance and obesity. Cell 2008;135:61–73
62. Bélanger C, Luu-The V, Dupont P, Tchernof A. Adipose tissue intracrinology: potential importance of local androgen/estrogen metabolism in the regulation of adiposity. Horm Metab Res 2002;34:737–745
63. Mayes JS, Watson GH. Direct effects of sex steroid hormones on adipose tissues and obesity. Obes Rev 2004;5:197–216
64. Tchernof A, Poehlman ET, Després JP. Body fat distribution, the menopause transition, and hormone replacement therapy [retracted in: Diabetes Metab 2006;32:285]. Diabetes Metab 2000;26:12–20
65. Johansen JA, Breedlove SM, Jordan CL. Androgen receptor expression in the levator ani muscle of male mice. J Neuroendocrinol 2007;19:823–826
66. Monks DA, O'Bryant EL, Jordan CL. Androgen receptor immunoreactivity in skeletal muscle: enrichment at the neuromuscular junction. J Comp Neurol 2004;473:59–72
67. Sinha-Hikim I, Taylor WE, Gonzalez-Cadavid NF, Zheng W, Bhasin S. Androgen receptor in human skeletal muscle and cultured muscle satellite cells: up-regulation by androgen treatment. J Clin Endocrinol Metab 2004;89:5245–5255
68. Ophoff J, Van Proeyen K, Callewaert F, et al. Androgen signaling in myocytes contributes to the maintenance of muscle mass and fiber type regulation but not to muscle strength or fatigue. Endocrinology 2009;150:3558–3566
69. Chambon C, Duteil D, Vignaud A, et al. Myocytic androgen receptor controls the strength but not the mass of limb muscles. Proc Natl Acad Sci U S A 2010;107:14327–14332
70. Fernando SM, Rao P, Niel L, Chatterjee D, Stagljar M, Monks DA. Myocyte androgen receptors increase metabolic rate and improve body composition by reducing fat mass. Endocrinology 2010;151:3125–3132
71. Semirale AA, Zhang XW, Wiren KM. Body composition changes and inhibition of fat development in vivo implicates androgen in regulation of stem cell lineage allocation. J Cell Biochem 2011;112:1773–1786
72. Nettleship JE, Jones RD, Channer KS, Jones TH. Testosterone and coronary artery disease. Front Horm Res 2009;37:91–107
73. Roger VL, Go AS, Lloyd-Jones DM, et al.; American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics—2012 update: a report from the American Heart Association. Circulation 2012;125:e2–e220

74. Basaria S, Coviello AD, Travison TG, et al. Adverse events associated with testosterone administration. N Engl J Med 2010;363:109–122
75. Glueck CJ, Richardson-Royer C, Schultz R, et al. Testosterone therapy, thrombophilia-hypofibrinolysis, and hospitalization for deep venous thrombosis-pulmonary embolus: an exploratory, hypothesis-generating study. Clin Appl Thromb Hemost 2014;20:244–249
76. Araujo AB, Dixon JM, Suarez EA, Murad MH, Guey LT, Wittert GA. Clinical review: Endogenous testosterone and mortality in men: a systematic review and meta-analysis. J Clin Endocrinol Metab 2011;96:3007–3019
77. Ohlsson C, Barrett-Connor E, Bhasin S, et al. High serum testosterone is associated with reduced risk of cardiovascular events in elderly men. The MrOS (Osteoporotic Fractures in Men) study in Sweden. J Am Coll Cardiol 2011;58:1674–1681
78. Svartberg J, von Mühlen D, Mathiesen E, Joakimsen O, Bønaa KH, Stensland-Bugge E. Low testosterone levels are associated with carotid atherosclerosis in men. J Intern Med 2006;259:576–582
79. Hak AE, Witteman JC, de Jong FH, Geerlings MI, Hofman A, Pols HA. Low levels of endogenous androgens increase the risk of atherosclerosis in elderly men: the Rotterdam study. J Clin Endocrinol Metab 2002;87:3632–3639
80. Akishita M, Hashimoto M, Ohike Y, et al. Low testosterone level as a predictor of cardiovascular events in Japanese men with coronary risk factors. Atherosclerosis 2010;210:232–236
81. Li L, Guo CY, Jia EZ, et al. Testosterone is negatively associated with the severity of coronary atherosclerosis in men. Asian J Androl 2012;14:875–878
82. Ammar EM, Said SA, Hassan MS. Enhanced vasoconstriction and reduced vasorelaxation induced by testosterone and nandrolone in hypercholesterolemic rabbits. Pharmacol Res 2004;50:253–259
83. Cavasin MA, Tao ZY, Yu AL, Yang XP. Testosterone enhances early cardiac remodeling after myocardial infarction, causing rupture and degrading cardiac function. Am J Physiol Heart Circ Physiol 2006;290:H2043–H2050
84. Crisostomo PR, Wang M, Wairiuko GM, Morrell ED, Meldrum DR. Brief exposure to exogenous testosterone increases death signaling and adversely affects myocardial function after ischemia. Am J Physiol Regul Integr Comp Physiol 2006;290:R1168–R1174
85. Friedl R, Brunner M, Moeslinger T, Spieckermann PG. Testosterone inhibits expression of inducible nitric oxide synthase in murine macrophages. Life Sci 2000;68:417–429
86. Ling S, Dai A, Williams MR, et al. Testosterone (T) enhances apoptosis-related damage in human vascular endothelial cells. Endocrinology 2002;143:1119–1125
87. McCrohon JA, Jessup W, Handelsman DJ, Celermajer DS. Androgen exposure increases human monocyte adhesion to vascular endothelium and endothelial cell expression of vascular cell adhesion molecule-1. Circulation 1999;99:2317–2322
88. Alexandersen P, Haarbo J, Byrjalsen I, Lawaetz H, Christiansen C. Natural androgens inhibit male atherosclerosis: a study in castrated, cholesterol-fed rabbits. Circ Res 1999;84:813–819
89. Liu J, Tsang S, Wong TM. Testosterone is required for delayed cardioprotection and enhanced heat shock protein 70 expression induced by preconditioning. Endocrinology 2006;147:4569–4577
90. Tep-areenan P, Kendall DA, Randall MD. Testosterone-induced vasorelaxation in the rat mesenteric arterial bed is mediated predominantly via potassium channels. Br J Pharmacol 2002;135:735–740
91. Tsang S, Wu S, Liu J, Wong TM. Testosterone protects rat hearts against ischaemic insults by enhancing the effects of alpha(1)-adrenoceptor stimulation. Br J Pharmacol 2008;153:693–709
92. Norata GD, Tibolla G, Seccomandi PM, Poletti A, Catapano AL. Dihydrotestosterone decreases tumor necrosis factor-alpha and lipopolysaccharide-induced inflammatory response in human endothelial cells. J Clin Endocrinol Metab 2006;91:546–554
93. Qiu Y, Yanase T, Hu H, et al. Dihydrotestosterone suppresses foam cell formation and attenuates atherosclerosis development. Endocrinology 2010;151:3307–3316
94. Nathan L, Shi W, Dinh H, et al. Testosterone inhibits early atherogenesis by conversion to estradiol: critical role of aromatase. Proc Natl Acad Sci U S A 2001;98:3589–3593
95. Lin AL, McGill HC Jr, Shain SA. Hormone receptors of the baboon cardiovascular system. Biochemical characterization of aortic and myocardial cytoplasmic progesterone receptors. Circ Res 1982;50:610–616
96. Liu PY, Death AK, Handelsman DJ. Androgens and cardiovascular disease. Endocr Rev 2003;24:313–340
97. Hanke H, Lenz C, Hess B, Spindler KD, Weidemann W. Effect of testosterone on plaque development and androgen receptor expression in the arterial vessel wall. Circulation 2001;103:1382–1385
98. Osterlund KL, Handa RJ, Gonzales RJ. Dihydrotestosterone alters cyclooxygenase-2 levels in human coronary artery smooth muscle cells. Am J Physiol Endocrinol Metab 2010;298:E838–E845
99. Marsh JD, Lehmann MH, Ritchie RH, Gwathmey JK, Green GE, Schiebinger RJ. Androgen receptors mediate hypertrophy in cardiac myocytes. Circulation 1998;98:256–261
100. Tsai HK, D'Amico AV, Sadetsky N, Chen MH, Carroll PR. Androgen deprivation therapy for localized prostate cancer and the risk of cardiovascular mortality. J Natl Cancer Inst 2007;99:1516–1524
101. D'Amico AV, Denham JW, Crook J, et al. Influence of androgen suppression therapy for prostate cancer on the frequency and timing of fatal myocardial infarctions. J Clin Oncol 2007;25:2420–2425
102. Beyer DC, McKeough T, Thomas T. Impact of short course hormonal therapy on overall and cancer specific survival after permanent prostate brachytherapy. Int J Radiat Oncol Biol Phys 2005;61:1299–1305
103. Bhasin S, Calof OM, Storer TW, et al. Drug insight: Testosterone and selective androgen receptor modulators as anabolic therapies for chronic illness and aging. Nat Clin Pract Endocrinol Metab 2006;2:146–159
104. Gao W, Dalton JT. Expanding the therapeutic use of androgens via selective androgen receptor modulators (SARMs). Drug Discov Today 2007;12:241–248
105. Kearbey JD, Gao W, Narayanan R, et al. Selective androgen receptor modulator (SARM) treatment prevents bone loss and reduces body fat in ovariectomized rats. Pharm Res 2007;24:328–335
106. Bhasin S, Jasuja R. Selective androgen receptor modulators as function promoting therapies. Curr Opin Clin Nutr Metab Care 2009;12:232–240
107. Dalton JT, Barnette KG, Bohl CE, et al. The selective androgen receptor modulator GTx-024 (enobosarm) improves lean body mass and physical function in healthy elderly men and postmenopausal women: results of a double-blind, placebo-controlled phase II trial. J Cachexia Sarcopenia Muscle 2011;2:153–161
108. Mohler ML, Bohl CE, Jones A, et al. Nonsteroidal selective androgen receptor modulators (SARMs): dissociating the anabolic and androgenic activities of the androgen receptor for therapeutic benefit. J Med Chem 2009;52:3597–3617
109. Flanagan J, Gray PK, Hahn N, et al. Presence of the metabolic syndrome is associated with shorter time to castration-resistant prostate cancer. Ann Oncol 2011;22:801–807
110. Gunter JH, Sarkar PL, Lubik AA, Nelson CC. New players for advanced prostate cancer and the rationalisation of insulin-sensitising medication. Intl J Cell Biol 2013;2013:834684
111. Conteduca V, Di Lorenzo G, Bozza G, Ardito R, Aieta M. Metabolic syndrome as a peculiar target for management of prostate cancer patients. Clin Genitourin Cancer 2013;11:211–220