Potential Side Effects of Androgen Deprivation Treatment in Sex Offenders

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Testosterone is an important hormone involved in sexual arousal, and, indeed, a profound reduction of testosterone levels may be helpful in controlling sexual impulses in sex offenders. Earlier thought of as a sex hormone only, testosterone has been increasingly shown to have manifold actions in the adult male. Normal adult levels of androgens are required for the health of bones, a large number of metabolic functions, mood, erythropoiesis, sebaceous gland activity of the skin, and several other functions. Severe androgen deficiency is associated with pathologies of these biological systems. Androgen deprivation therapy may result in osteoporosis, weight gain with an increased visceral adiposity, impaired glucose tolerance, dyslipidemia, and emotional disturbances. Some of these features combine in the metabolic syndrome that is also frequently associated with the use of psychotropic medication in general. It leads to a moderately increased risk of fractures and diabetes mellitus (by 40%–50%), and a small increased risk of cardiovascular morbidity and depression (by 10%–20%). It should be noted that small proportionate increases in risk may be of modest clinical significance when background risks are very low. Effective and safe management of sex offenders treated with testosterone-deprivation therapy should include careful monitoring of side effects and their prevention and treatment.

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In post-pubescent males with circulating testosterone levels in the normal range, testosterone plays an important role in their sexual interest and associated sexual arousability, which is defined as a state that motivates the individual toward the experiences of sexual pleasure and possibly orgasm.[1] Consequently, a reduction in circulating testosterone may be helpful in reducing sexual interest, arousability, fantasies, and behavior.[2] This principle has been put into practice in the treatment of sex offenders.[3–6] Higher serum testosterone levels have been found to be associated with more invasive sexual crimes in convicted adult male sex offenders, and serum testosterone also predicts sexual recidivism.[7]

Several pharmacological agents have been used to achieve a high degree of depletion of androgens: medroxyprogesterone acetate (MPA), cyproterone acetate (CPA), and gonadotropin-releasing hormone agonists or analogues (GnRHa; such as buserelin [Suprefact]; leuprorelin [Lucrin, Eligard]; goserelin [Zoladex], and tryptorelin [Decapeptyl]). MPA and CPA are synthetic progesterones that, through negative feedback on the pituitary, reduce the circulating levels of luteinizing hormone and testosterone. CPA also competes with the androgen receptor. GnRHa compounds initially overstimulate luteinizing hormone-releasing hormone receptors and increase testosterone secretion. But this effect is short lived and a desensitization of luteinizing hormone receptors ensues, which also decreases luteinizing hormone and subsequent testosterone secretion. GnRHa compounds are administered as periodic injections or subcutaneous implantations.

There is growing insight into the role of androgens in male physiology. Testosterone was formerly often thought of as a sex hormone only (i.e., a hormone for male reproduction, stimulating sexual interest and arousal), but it is becoming increasingly clear that the actions of testosterone are manifold in the adult male (for a review, see Ref. 8). Normal adult levels of androgens are required for the health of bones, a large number of metabolic aspects, mood, erythropoiesis, sebaceous

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gland activity of the skin, and several other functions. Severe androgen deficiency is associated with pathologic effects on these biological systems. In this article, we address several of the side effects of androgen deprivation treatment (ADT) of adult men, and not the compound-specific side effects. Much of the information has been gleaned from another disease requiring ADT, mainly hormone-sensitive prostate cancer.

Despite the availability of nonpharmacological treatment options (e.g.. cognitive–behavioral treatment) for sex offenders, the overall effectiveness on the sexual offense recidivism rate is modest (absolute risk reduction for recidivism sexual offense, 4.5%; odds ratio, 0.81; 95% confidence interval, 0.71–0.94).[9] Moreover, the potential effectiveness is still debatable, due to shortcomings in the methodology of treatment studies (e.g., few studies used a randomized design). Especially for offenders who refuse treatment or drop out, psychological treatment may be unsuccessful in reducing the risk of recidivism. Therefore, ADT for sex offenders is sometimes considered by psychiatrists. Although articles addressing treatment of sex offenders with antiandrogens report side effects,[4,10–12] the awareness of side effects on bone mineral density and metabolism is not high. Psychiatrists are generally not familiar with the recent insights into the effects of ADT. With information available that long-term ADT affects the health of those who undergo such treatment, evidence of the harmful effects can no longer be ignored. Physicians must adhere to the injunction: first, do no harm.[13] A parallel may be drawn with the urologist treating a prostate cancer patient with ADT. In the beginning of this type of pharmacological treatment, the awareness of the side effects was low, but increasing attention has been focused on the impact on general health of hormone intervention, and the patient should be informed of these effects. The problem is even more pressing in the case of sex offenders, who are usually younger than men suffering from prostate cancer and who are likely to develop more severe side effects due to their much longer-term ADT. Thus, an effort should be made to inform the sex offenders of the adverse effects of ADT, so that they can adequately consent and participate.

Effects of ADT on Bone Mineral Density and Fracture Risk

Administration of drugs such as MPA, CPA, and GnRHa induces a profound decline in the levels of sex steroids in men, not only of testosterone but also of estradiol. Traditionally, conceptualized as female hormones, estrogens appear to have significant effects on the male biological system.[14] Favorable effects have been noted on bone, brain, and cardiovascular physiology. Estrogens in the male are predominantly the products of peripheral aromatization of testicular and adrenal androgens, and they produce significant beneficial effects on skeletal growth and bone maturation. In old age, estrogen levels are better predictors of bone fractures than are androgen levels.

ADT is followed by rapid bone loss, typically in the spine, hip, and forearm, similar to the loss of skeletal integrity in women after surgical ovariectomy or during early menopause. Bone mineral density decreases within 1 year after ADT (Table 1),[4,15–17] with a continuing decrease causing bone loss thereafter. Lumbar spine bone density decreases approximately three to seven percent per year, but there is also bone loss, albeit to a lesser extent, at appendicular skeletal sites such as the femoral neck. In a study of 12 males (aged 28 $\pm$ 6 years) who had undergone bilateral orchidectomy following sexual offenses, the mean bone loss was seven percent per year (over the first 2 years).[19] In these patients, additional bone loss after ADT increases their risk of osteoporotic fractures.[20–22] In addition to the decline in bone density, ADT induces changes in body composition, including increases in weight and body mass index, and decreases in lean body mass and muscle mass/strength,[17,23,24] which may increase the risk of falls, further enhancing the risk of fractures. Decreasing muscle strength may also directly decrease bone mass. It has been estimated in patients with prostate cancer that the relative risk of fractures is increased by 45 percent (Table 1) and that the number needed to cause harm for an occurrence of a fracture one to five years after initiation of ADT was 28 for those treated with GnRHa.[21] This finding implies that, when 28 subjects are exposed to ADT, on average, one patient will experience a fracture who would not otherwise have been harmed. It is therefore recommended that bone mineral density be measured by dual energy x-ray absorptiometry (DEXA) before the start of ADT, to detect preexisting osteoporosis and to monitor significant bone loss over time.

While ADT in sex offenders may be a therapeutic imperative, there are treatments that can ameliorate

Table 1 Estimated Risks for Selected Side Effects of Androgen Deprivation Therapy in Men

Side Effects	Duration of Deprivation	Percent Change or Hazard Ratio
Bone mineral density and fracture risk		
Bone mineral density	6 months	−3.5%[17]
	12 months	−5.3%[15]
	12 months	−3.3%[16]
	12 months	−4.9% and −6.8%[4]
Any fracture*	5 years	1.45 (95% CI: 1.36–1.56)[21]
Fracture resulting in hospitalization*	5 years	1.66 (95% CI: 1.47–1.87)[21]
Glucose and lipid metabolism		
Weight and body mass index	6 months	+0.8%[17]
	11 months	+2.4%[23]
Fat body mass	3 months	+8.4%[18]
	11 months	+9.4%[23]
Lean body mass	3 months	−2.8%[18]
	11 months	−2.7%[23]
Muscle area	11 months	−3.2%[23]
Total cholesterol level	6 months	+6.1%[17]
	11 months	+9.0%[23]
High-density lipoproteins cholesterol level	11 months	−11.3%[23]
Low-density lipoproteins cholesterol level	11 months	+7.3%[23]
Triglyceride level	6 months	+8.2%[17]
	11 months	+27%[23]
Fasting insulin level	3 months	+64%[18]
Incident diabetes	4.6 years	1.44 (95% CI: 1.34–1.55)[32]
Incident coronary heart disease	4.6 years	1.16 (95% CI: 1.10–1.21)[32]
Incident myocardial infarction	4.6 years	1.11 (95% CI: 1.01–1.21)[32]
Incident sudden cardiac death	4.6 years	1.16 (95% CI: 1.05–1.27)[32]
Mood disturbances		
Depression (or other affective disorder)	4.3 years	1.08 (95% CI: 1.02–1.15)[49]
Constitutional symptoms (e.g., fatigue, malaise, anorexia, abnormal weight gain, debility)	4.3 years	1.17 (95% CI: 1.13–1.22)[49]

*Among those receiving nine or more doses of gonadotropin-releasing hormone agonist in the first 12 months after diagnosis of prostate cancer.

bone loss. Although the efficacy of calcium and vitamin D supplementation in osteoporosis prevention has not been studied in men on ADT, they are likely to benefit from calcium (1200–1500 mg daily) and vitamin D supplementation (400–800 IU daily), and should be advised to abstain from smoking and excessive alcohol use. A class of drugs, the bisphosphonates (e.g., oral alendronate or risedronate, and parental pamidronate or zoledronic acid given every 12 weeks), inhibit bone resorption by their inhibitory effects on osteoclast activity. These drugs have been successfully used in reducing bone loss in patients receiving antiandrogens.[24–27] Alendronate was found to reduce the incidence of vertebral fractures in men in randomized double-blind trials,[28,29] but as yet there have been no randomized trials of reduction in fracture rates in men treated with ADT. Nevertheless, the use of bisphosphonates is recommended in men with DEXA-proven osteoporosis or in men with osteopenia and pre-existing bone insufficiency fractures (due to minimal trauma). It should further be considered when there is evidence of progressive bone loss during ADT. Considering the role of estrogens, also in male bone health, selective estrogen receptor modulators such as raloxifene are also being investigated.[30,31]

Effects of ADT on Glucose and Lipid Metabolism

In a population-based cohort of elderly men with prostate cancer with follow up of up to 10 years, ADT increased the risks of developing diabetes mellitus (by 44%) and the mortality of cardiovascular diseases (by 16%; Table 1).[32] These adverse findings may be partially mediated through effects on glucose and lipid metabolism with an increased risk of the metabolic syndrome. It was found that men treated with ADT develop an increase in body and fat mass, hyperinsulinemia, hyperglycemia, and insulin resistance (measured by the HOMA IR technique),[17,23,24,33,34] and an impaired lipid pro-

file.[34,35] ADT increased circulating levels of low-density lipoprotein, total cholesterol, and triglycerides.[24,34,35] In addition, large prospective studies have shown that low testosterone levels predict development of type 2 diabetes in men.[36–39] Two studies demonstrated a positive relationship between total testosterone levels and insulin sensitivity in normal[40] and diabetic men.[41] A recent study demonstrated a positive correlation between serum testosterone levels and insulin sensitivity in men across the full spectrum of glucose tolerance.[42] In this study, men with hypogonadal testosterone levels were twice as insulin resistant as their eugonadal counterparts, and 90 percent fulfilled the criteria for metabolic syndrome. One of the characteristics of metabolic syndrome is insulin resistance. Insulin resistance has assumed increasing importance as a risk factor for cardiovascular disease. A report on two patients receiving ADT for prostate cancer showed deterioration of glycemic control.[43] In one case, the patient had diabetes mellitus type 2, and the other patient developed diabetes mellitus after beginning ADT. This observation indirectly substantiates the notion that ADT leads to insulin resistance.

To reduce the risk of the metabolic syndrome, it is important to adopt a healthful lifestyle and dietary behaviors,[44] including smoking cessation and regular exercise. Such nonpharmacological interventions can be followed by statins that lower blood low-density lipoprotein levels and reduce the risk of cardiovascular events. The effects are not confined to patients with cardiac disease, but are also present in diabetics, in whom first major cardiovascular events were reduced by 37 percent.[45] ADT probably increases cardiovascular risk by a multifactorial mechanism including insulin resistance, and therefore target levels for lipids should be more stringent than those recommended for the general population. The following target levels are therefore derived from research in type 2 diabetes: low-density lipoprotein cholesterol level, $<$2.6 mmol/L (100 mg/dL); fasting triglycerides levels, $<$1.7 mmol/L (150 mg/dL); and high-density lipoprotein cholesterol, $>$1.1 mmol/L (40 mg/dL).[46]

Effects of ADT on Mood Disturbances

Low androgen levels have been associated with a small increased risk of depression (by 8%, Table 1).[47–49] Presumably, mood disorders and depression will be diagnosed by the attending mental health professional, but it is pertinent to associate mood disorders with ADT. Sexual dysfunction, emotional disturbances, anxiety, fatigue, malaise, memory difficulties, asthenia, lack of drive, and listlessness—termed the androgen-deprivation syndrome—have been reported as side effects of ADT, with an increased relative risk of about 17 percent over at least five years.[4,49,50] The effects of ADT on mood have also been tested in double-blind, placebo-controlled trial. Although testosterone levels were markedly suppressed, there were only slight increases in depressive symptoms on the group level, although one subgroup of men (10%–15%) showed clinically relevant increases in reported symptoms (as assessed by the Beck Depression Inventory).[2] It is plausible that negative effects on mood induced by long-term hypogonadism are more prevalent among sex offenders than those in the selected group of healthy young men who received GnRHa for only four weeks.

It should further be taken into account that sexual violence is more likely to be committed by individuals with paraphilia and comorbid affective disorders or other mental illness.[51] For example, sex offenders suffering from hypomania (which can be accompanied by excessive sexual arousal and sexually disinhibited behavior), may be at an increased risk of bipolar depression after the start of ADT. Moreover, conviction, imprisonment, and the stigma and shame of being a sex offender may also increase the risk of depression. Sex offenders should therefore be carefully evaluated before the start of and during ADT for the presence of a mental illness, to provide appropriate psychiatric treatment.

Other Side Effects of ADT

ADT leads to hot flushes and night sweating in most men, which may reduce quality of life.[2,4,24] Hot flushes can be effectively treated with megestrol acetate,[52] and selective serotonin reuptake inhibitors (SSRIs) and selective serotonin-norepinephrine reuptake inhibitors (SSNRIs), which also may be beneficial in treating comorbid depressive symptoms. Moreover, ADT reduces hemoglobin and hematocrit levels.[17,53] This reduction usually has no major impact on a person's health, unless cardiac or pulmonary functions are marginal.

Profound ADT reduces sebaceous gland activity in the skin, often leading to dry skin and brittle nails.[54] Symptoms such as itching and skin tears can be very bothersome. They usually can be remedied

by topical application of moisturizing creams. Moreover, facial and body hair growth is reduced by ADT (i.e., feminization).[4]

Other side effects that have been described are migraine, leg (muscle) cramps, phlebitis, vertigo, elevation of blood pressure, gastrointestinal complaints, gallbladder stones, thromboembolic complications (deep vein thrombosis), breast tenderness, and gynecomastia (i.e., breast growth, especially when using CPA).[10,55] Besides impotence and its libido-reducing effects, ADT also directly induces partial azoospermia and infertility, although it provides no birth control assurance.

Conclusions

ADT can be an affective treatment for some sex offenders or men with uncontrollable sexual impulses at risk of becoming sex offenders. Yet, sex offenders who start treatment with ADT should know that this intervention is not without risks (Table 1). Although many questions remain, current evidence indicates that there is a moderately increased risk of fractures and diabetes mellitus (by 40%–50%) and a small increase (by 10%–20%) in the risk of cardiovascular morbidity and depressive symptoms. The patient should be evaluated for these risks which may require consultation with an internist or endocrinologist with expertise on the metabolic syndrome and bone disease. The risk assessment should include inquiry about prior fractures and cardiovascular events, family history of osteoporosis and cardiovascular disease, alcohol consumption, and smoking habits (Table 2). Men should start calcium and vitamin D supplementation. Bisphosphonates can be considered in men with documented osteoporosis. Besides lifestyle interventions (diet and exercise), statins can be considered to counteract the detrimental effects on the lipid profile and reduce cardiovascular risk.

The present-day approach is a total depletion of circulating testosterone. There is as yet limited information on dose-response relationships between testosterone and sexual behavior.[56] Antiandrogens such as the androgen receptor antagonists flutamide, nilutamide, and bicalutamide, do not lead to total androgen depletion. Further studies are therefore necessary to examine whether lower treatment doses and modern antiandrogens also effectively reduce aberrant sexual behavior, but have fewer side effects on bone mineral density and metabolism.

Table 2 Recommended Clinical Assessment of Men Before the Start of Androgen Deprivation Therapy and During Follow-up

Risk assessment before the initiation of ADT:
History taking: prior fractures, prior cardiovascular events, family history of osteoporosis and cardiovascular disease, alcohol consumption, and smoking habits
Rule out or treat affective disorders
Advise lifestyle modification, including weight-bearing exercise, healthful dietary pattern, and abstinence from smoking and excessive alcohol use
Physical examination: especially weight, height, blood pressure
Complete laboratory screen, with fasting glucose (to detect incident diabetes), lipid profile, hemoglobin, and hematocrit level
DEXA
Clinical assessment after the initiation of ADT:
History taking and physical examination (every six months): especially evaluate for signs and symptoms of weight gain, hypertension, hot flushes, depression, emotional disturbances, and other constitutional symptoms
Laboratory examination: fasting glucose, lipid profile, hemoglobin, and hematocrit level
DEXA (every one or two years)

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