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The effect of estrogen on the sexual interest of castrated males: Implications to prostate cancer patients on androgen-deprivation therapy

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Contents

Abstract

Androgen deprivation therapy (ADT) for prostate cancer (PCa) treatment causes sexual dysfunction. We review here the effects of estrogen on the sexual performance of androgen-deprived males. The major findings are:

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1. Estrogen receptors are present in brain centers that are important for sexual behavior; as well as in male reproductive organs, in a pattern suggesting that estrogen may have some role in orgasmic function and genital skin sensitivity.
2. Estrogen restores sexual interest above castrate levels in many vertebrates including reptiles, birds and mammals; but multiple factors contribute to the magnitude of this effect.
3. Data from castrated men, aromatase-deficient men, male-to-female transsexuals, and men on antiandrogens all suggest that estrogen can maintain some libido in androgen-deprived men.

We discuss the general benefits of estrogen therapy to quality of life of men on ADT, the potential risks of this treatment, and possible treatment regimes for estrogen therapy in males. Unless contraindicated, we propose that PCa patients on ADT would benefit from supplemental parenteral estrogen.

Keywords: Androgen deprivation therapy; Prostate cancer; Libido; Estrogen; Male sexual function; Castrated animals; Orgasm; Skin sensitivity

1. Introduction

There are various situations where genetic males are therapeutically androgen-deprived. The most common reason for androgen deprivation therapy (ADT) is to slow down prostate cancer (PCa)'s growth. In addition, as part of sex reassignment surgery, male-to-female transsexuals (MtFs) are also androgen-deprived. ADT can be achieved by either surgical or chemical castration. Currently, luteinizing hormone-releasing hormone (LHRH) agonists are the most frequently used agents for ADT in the PCa patient population. However, other agents including high-dose estrogen (E), high-dose ketoconazole, abiraterone, and LHRH antagonists can also be used to achieve a castrate level of testosterone. Single-agent antiandrogen therapy is also used as a form of ADT, but does not lower serum testosterone levels.

In most cases, ADT impedes sexual function; reducing libido and causing erectile dysfunction [1]. These effects distress patients and psychologically impact their intimate partners, reducing the quality of life for both [2]. While treatments for erectile dysfunction are available, currently there is no treatment for loss of libido subsequent to ADT. Yet, loss of erections due to ADT does not mean a cessation in sexual activity [3]. For example, men can still achieve orgasm without an erect penis.

ADT not only depletes androgens in men, but also estrogens. This is because estrogen in males is derived from testosterone. Some males on ADT receive E therapy. For MtFs, E therapy can aid in body feminization (breast development) and, for PCa patients, supplemental E can alleviate some of the more intense adverse events, such as hot flashes [4]. Additional benefits of E treatment for androgen-deprived men include improving bone mineral density [5] and lipid profiles [6]. In one study, treatment with E also improved some aspects of cognitive function [7].

Previously we reviewed papers suggesting that E can, to some extent, elevate sexual interest in castrated males [8]. We have since confirmed this with a study of castrated male rats with and without estradiol (E2) treatment [9]. Here, we provide a more extensive literature review on how E influences sexual interest in androgen-deprived males for a wealth of species, ranging from amphibians to mammals including humans. In addition, we discuss the potential effect of E on peripheral tissues that are related to sexual function, such as genital skin and pelvic floor muscles that are important in achieving an orgasm. We then discuss the pros and cons of E therapy as well as various dosing regimes—factors that need to be considered in clinical settings.

2. Estrogen receptors

E induces its effects by acting on estrogen receptors (ERs) that are widely distributed throughout the body. In the tetrapod brain, ERs are present in areas that control male sexual behavior, most notably the medial preoptic area, medial amygdala and the bed nucleus of stria terminalis [10,11]. Intracranial E implants in those specific areas of the brain have been shown implicitly to increase sexual behavior in castrated males of many vertebrate species (see Suppl. Tables 1 and 2). The equivalent brain areas in humans also express ERs. Replicating the results observed in animals by implanting E into human brains would be excessively invasive; however, there is evidence that castrated men on E therapy maintain better libido than those not receiving supplemental E [8].

The mechanism for how E elevates sexual interest in castrated men has not been extensively investigated. In imaging studies, the preoptic area and medial amygdala are activated during sexual arousal by both visual [12] and olfactory stimulation [13,14] although not necessarily by tactile stimulation [15]. However, no study has explored if these activation patterns in response to sexual stimuli change after E treatment in androgen-deprived men.

E may also influence sexual behavior by acting on peripheral tissues. Indeed, ERs are present in male reproductive organs although their function remains enigmatic [16]. They may not be related to erectile function per se because in both castrated men and other male mammals, E treatment does not restore erectile function. We discuss in later sections how E may potentially modulate pelvic floor muscle function and genital skin physiology.