Clinical Use of Aromatase Inhibitors in Adult Males

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ABSTRACT

Introduction. There is a growing interest in the treatment of late-onset hypogonadism, another name for the study of testosterone deficiency in an older age group. Initial attempts at testosterone replacement have also brought attention to the possible adverse effects on the patients' cardiovascular risk factors and their prostate health. The "female" hormone estradiol is no longer considered as the feminizing hormone, as it has been identified to have an effect on the sexual and general well-being of adult males. Urologists and endocrinologists alike have started to pay attention to the serum T/E_2 (testosterone : estradiol) ratio that appears to be more important than the respective individual hormonal levels. Therein lies the possible role of aromatase inhibitors (AIs) in restoring the normal balance of serum testosterone and estradiol levels for the adequate treatment of late-onset hypogonadism, while limiting the potential adverse effects. Currently, other established clinical indications of AIs include the treatment of breast cancer in female patients and developmental growth problems in pediatric patients.
Aim. This review evaluates the role of AIs as a treatment option for late-onset hypogonadism and the evidence for its other clinical uses in men, including its possible adverse effects.
Methods. A literature review was performed with regards to the use of aromatase inhibitors in adult males, the role of estrogens in adult males, as well as adverse effect of AIs on bone health in adult males.
Main Outcome Measures. To evaluate the evidence for the use of AIs in adult males to treat late-onset hypogonadism, obesity-related hypogonadotropic hypogonadism, gynecomastia, and male subfertility.
To evaluate the evidence for the possible adverse effects on the bone health of adult males with the use of AIs.
Results. Currently there is no literature to recommend the use of AIs in adult males to treat late-onset hypogonadism, obesity-related hypogonadotropic hypogonadism, gynecomastia, or male subfertility, although some positive effects have been reported. The adverse effects on bone health seen in females treated with AIs are not seen in males.
Conclusions. With the better understanding of the T/E_2 ratio in adult males, the lack of scientific data to show that bone health is adversely affected by AI usage in adult males, the positive effects of AIs on the treatment of conditions like late-onset hypogonadism and male subfertility encourages conducting large-scale, multicenter, randomized controlled trials for the clinical use of AIs in adult males. **Tan RBW, Guay AT, and Hellstrom WJG. Clinical use of aromatase inhibitors in adult males. Sex Med Rev 2014;2:79–90.**

Key Words. Late-Onset Hypogonadism; Testosterone Deficiency; Aromatase Inhibitors; Testosterone : Estradiol Ratio; T/E_2 Ratio; Low Testosterone

Introduction

Interest in the benefits of androgen replacement in males began as early as the end of the 19th century. Dr. Charles E. Brown-Sequard, Professor of Experimental Medicine at the College de France, made a presentation to the Societe de Biologie in June of 1889 with reports of his own observations on improved physical strength, intellectual capacity, and sexual vigor after repeated self-administration of a watery extract *liquide testiculaire* prepared from animal gonads [1]. Although we now know that Dr. Brown-Sequard's perceived clinical improvements were probably

due to a placebo effect (as testosterone is not water soluble), his presentation did ignite the first flames for the continued research of testosterone replacement in males. It was not until 1935, when three independent research teams led by Adolf Butenandt, Karoly Gyula, and Leopold Ruzicka (sponsored by Schering, Organon, and Ciba, respectively) were successful in its synthesis, that this powerful testicular hormone that "when injected into castrated animals would restore their maleness" [2] was ultimately named testosterone. Subsequently, Butenandt and Ruzicka received the Nobel Prize for Chemistry in 1939 for their seminal work on androgens.

Testicular function declines with advancing age [3], but unlike in menopause, where the ovary undergoes rapid functional involution, the change is incremental and of the same magnitude as that of other organs of the body [4]. The rate of serum testosterone decline is approximately 1% per year [5,6], once a man reaches his third decade of life. Understanding of the hypothalamic–pituitary–gonadal (HPG) axis brings to light the negative feedback that testosterone exerts on the hypothalamus and pituitary gland. In normal adult males, neurons in the preoptic area and the medial basal region of the hypothalamus secrete gonadotropin releasing hormone (GnRH), which in turn determines the pattern of secretion of the gonadotrophins, luteinizing hormone (LH), and follicle stimulating hormone (FSH), from the anterior pituitary gland. LH acts on the Leydig cells in the testis to produce testosterone whereas FSH regulates spermatogenesis in the basal aspect of the plasma membrane of Sertoli cells in the testis. Testosterone, along with its aromatized product, estradiol, then acts in a negative feedback mechanism on the anterior pituitary as well as the hypothalamus. Contrary to the traditional belief that estradiol is only important to female physiology, there is evidence that estradiol signaling via the HPG axis plays an important role in controlling GnRH and gonadotropin secretion in men. There are as many estradiol receptors as testosterone receptors in the hypothalamus and pituitary gland. This came from the observation of suppressed gonadotropins and low testosterone in men with estrogen-secreting tumors [7] and the profound inhibition of gonadotropin secretion via decreased pituitary response to GnRH with pharmacologic administration of estrogen or industrial exposure to diethylstilbesterol (DES) [8]. Estradiol is 200 times more potent as an inhibitor of gonadotropins when compared with testosterone. In males,

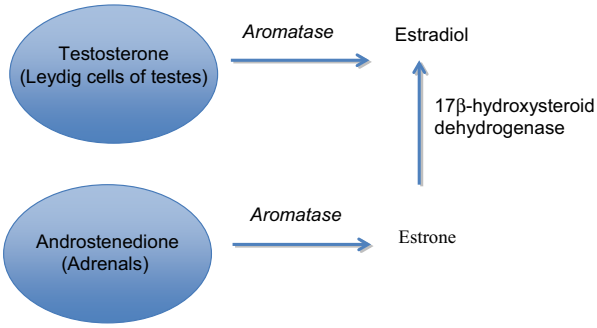

Figure 1 Sources of estradiol in men.

estradiol is primarily produced via peripheral aromatization of serum testosterone with the Leydig cells contributing 20% of the total serum estradiol. The adrenals contribute an even smaller percentage from the aromatization of androstenedione into estrone, of which a small portion is converted to estradiol [9]. The enzyme responsible for the peripheral conversion of testosterone to estradiol is known as the aromatase (Figure 1). The important contribution of estrogens to male health and the possible clinical use of aromatase inhibitors (AIs) in men derive from observations from case reports of men with aromatase deficiency and aromatase excess. Adult aromatase-deficient men demonstrate a remarkably low bone mass and unfused epiphyses leading to linear growth into adulthood and above-average body length. Bone has both testosterone and estradiol receptors. Both need to be stimulated to have normal bone metabolism. Estradiol regulates bone resorption and testosterone stimulated fibroblastic bone matrix formation. Once treated with estradiol, epiphyses close, bone mineral density (BMD) increases, and related metabolic disturbances improve in most of these patients [10]. Conversely, men with aromatase excess have the phenotype of gynecomastia, accelerated growth, and premature bone maturation during puberty due to excessive peripheral estrogen synthesis.

AIs could then be used to treat or prevent gynecomastia and increase gonadotropin secretion. Thereby stimulating Leydig and Sertoli cell function and prevent or delay epiphyseal closure, which increases adult height [11].

Estrogens in Males

Demographic factors that influence serum estradiol levels in males include age, body mass index (BMI), and race. Most studies report an