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Review article

Serum testosterone levels after medical or surgical androgen deprivation: A comprehensive review of the literature

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Abstract

Androgens and the androgen receptor play a role in the progression of prostate cancer. Androgen deprivation therapy (ADT) is a mainstay in the treatment of metastatic prostate cancer. ADT is expected to reduce serum testosterone levels from a normal level of about 500 to 600 ng/dl (17.3–20.8 nmol) down to castration levels. Traditionally, castration was considered to be achieved if testosterone levels were lowered to a threshold of 50 ng/dl (1.73 nmol/l), a definition determined more by measurement methods derived from the use of old assay methods than by evidence. Serum testosterone levels in three-quarter patients after surgical castration drop to less than 20 ng/dl (0.69 nmol/l). Ineffective suppression of testosterone is currently poorly recognized and may possibly have an effect of prostate cancer mortality. Persistent levels of serum testosterone after castration are mainly derived from adrenal androgens. Furthermore, the arrival of new therapies targeting androgen synthesis and androgen receptor activity has renewed interest on serum testosterone. This review discusses the biosynthetic pathway for androgen synthesis in humans and provides a comprehensive review of serum testosterone levels after surgical or medical castration. This review assesses serum testosterone levels after surgical castration and different pharmacologic castration in patients with prostate cancer under ADT, and ineffective testosterone suppression. The author proposes methods to better lower serum testosterone levels during ADT.

Keywords: Prostate cancer; Androgen deprivation therapy; Androgen metabolism; Serum testosterone

1. Introduction

Androgens and the androgen receptor (AR) have been implicated in prostate cancer progression. Huggins and Hodges in 1941 demonstrated that bilateral orchiectomy or estrogen treatment is an effective treatment for prostate cancer [1]. Based on their findings, androgen deprivation therapy (ADT) by bilateral orchiectomy or the use of gonadotropin-releasing hormone (GnRH) agents (GnRH agonists, used as a synonym of luteinizing hormone-RH [LHRH] agonists, and GnRH antagonists) has remained the main therapeutic option for patients with metastatic prostate cancer for about 70 years. ADT is expected to reduce serum testosterone levels from a normal level of about 500 to 600 ng/dl (17.3–20.8 nmol/l) down to castration levels. Both methods can suppress circulating testosterone levels by 90% to 95%, and most treated men with advanced prostate cancer would have an objective disease response, including a decrease in prostate-specific antigen (PSA). ADT can be utilized in these patients to reduce tumor burden, alleviate symptoms, and prolong overall survival. However, while providing symptom palliation and disease control, ADT is not curative. These treatments exert selection pressure that contributes to the emergence of prostate cancer cells that can proliferate and thrive despite the castrate levels of testosterone. Most patients would experience disease progression after 12 to 24 months of treatment, which is evidenced by increasing PSA, radiologic progression, or progression of disease-related symptoms [2–5].

In men with prostate cancer, bilateral orchiectomy reduces serum testosterone to castrate levels within 12 hours [6]. The clinical significance of different serum levels of testosterone yielded during ADT has not yet been well elucidated. The serum testosterone levels in men being treated with ADT aiming at castrate testosterone levels have never been categorically established [7]. Historically, castration was considered to be achieved if testosterone levels were lowered to a threshold of 50 ng/dl (1.73 nmol/l), a

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definition determined more by measurement methods derived from the use of old assay methods than by evidence [8]. Ineffective testosterone suppression after a period of adequate suppression is currently poorly recognized and may result in increased prostate cancer mortality. Furthermore, the arrival of new therapies targeting androgen synthesis and AR activity, such as abiraterone and enzalutamide (formerly known as MDV3100), has also focused renewed interest on serum testosterone [9,10].

This review discusses the biosynthetic pathway for androgen synthesis in humans and provides a comprehensive review of serum testosterone levels after surgical or medical castration. This review assesses serum testosterone levels after surgical castration and different pharmacologic castration in patients with prostate cancer under ADT, and ineffective testosterone suppression. The author proposes methods to better lower serum testosterone levels during ADT.

2. Androgen metabolism in humans

In human males, testosterone is the major circulating androgen (Fig. 1). More than 95% of testosterone is secreted by the Leydig cells, whereas the adrenal cortex also contributes to this production [11,12]. The Leydig cells produce testosterone in response to hormonal stimulation by LH. Testosterone plays a key role in the development of male reproductive tissues, such as the testis and prostate, as well as in promoting secondary sexual characteristics such as increased muscle, bone mass, and the growth of body hair [13]. In addition, testosterone is essential for health and well-being as well as the prevention of osteoporosis [14,15]. Serum testosterone levels decline with advancing age [16].

The adrenal androgen pathway is not entirely affected by current routine ADT. Biosynthetic pathway for adrenal androgen synthesis is Δ-5 pathway in primates like humans (Fig. 1) [17]. Steroid 17α-hydroxylase/17,20-lyase (CYP17A1—cytochrome P450, family 17, subfamily A, polypeptide 1) is localized in endoplasmic reticulum membranes of steroidogenic cells. CYP17A1 catalyzes the 17α-hydroxylation reaction of Δ4-C21 steroids (progesterone derivatives) and Δ5-C21 steroids (pregnenolone derivatives) as well as the 17,20-lyase reaction producing C19-steroids, a key branch point in steroid hormone biosynthesis. Depending on CYP17A1 activity, the steroid hormone biosynthesis pathway is directed to either the formation of mineralocorticoids and glucocorticoids or sex hormones [18]. The first activity gives hydroxylation of pregnenolone and progesterone at the C(17) position to generate 17α-hydroxypregnenolone and 17α-hydroxyprogesterone, whereas the 17,20-lyase activity cleaves the C(17)-C(20) bond of 17α-hydroxypregnenolone and 17α-hydroxyprogesterone to form dehydroepiandrosterone (DHEA) and androstenedione, respectively. The modulation of these 2 activities occurs through cytochrome b(5) [19]. A subset of androgens, adrenal androgens, include any of C19-steroids synthesized by the adrenal cortex, that function as weak androgens or androgen precursors, including DHEA, its sulfate, DHEA sulfate (DHEA-S), and androstenedione [20]. As a result, a large amount of DHEA and DHEA-S are in blood in humans and nonhuman primates. The synthesis and secretion of the adrenal androgens DHEA

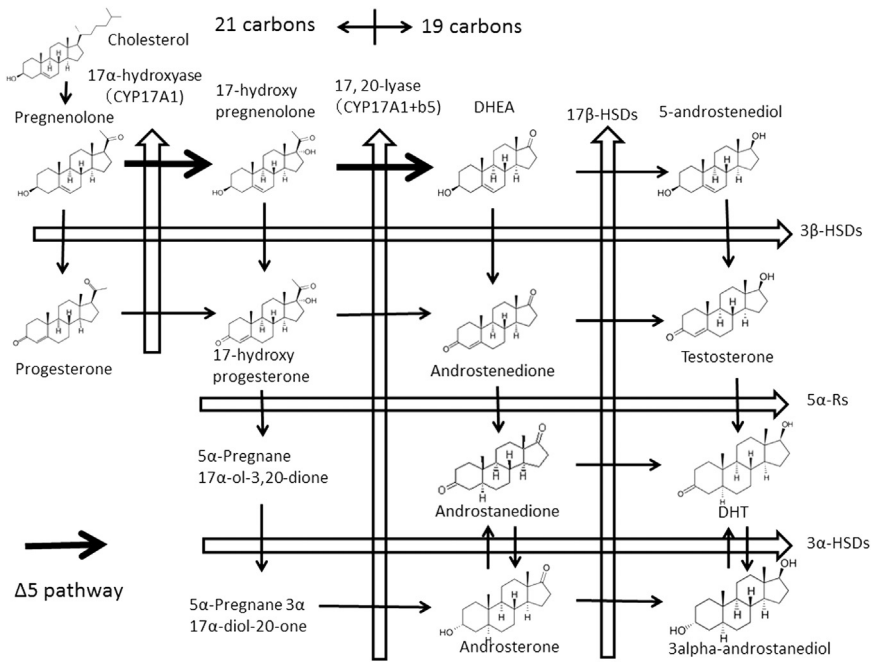

Fig. 1. The androgen metabolic pathway and enzyme-related products of human being. Biosynthetic pathway for androgen synthesis is the Δ-5 pathway in primates like humans. As a result, a large amount of DHEA and DHEA-S is in the serum in humans. b5 = Cytochrome-b5 reductase; HSD = hydroxysteroid dehydrogenase; 5α-Rs = 5α-reductases.