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Urologic Oncology: Seminars and Original Investigations 33 (2015) 407–412

UROLOGIC ONCOLOGY

Review article

Hypogonadism and fertility issues following primary treatment for testicular cancer

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Received 28 October 2014; received in revised form 14 December 2014; accepted 18 January 2015

Abstract

Background: The majority of testicular cancer (TC) patients are cured and expected to live for decades after treatment, such that knowledge about hypogonadism and fertility issues is particularly important for the group of testicular cancer survivors (TCSs). Hypogonadism and fertility issues are related to treatment intensity.

Methods: In order to give an overview about hypogonadism in testicular cancer survivors (TCSs) the literature was reviewed. Testicular dysfunction was defined as inadequate spermatogenesis, as reflected by increased levels of Follicle Stimulating Hormone (FSH) and reduced fertility and/with or without insufficient testosterone (T) production with or without compensatory increased Luteinizing Hormone (LH) levels.

Findings: Hypogonadism may lead to reduced sexual functioning and well-being, fertility problems, muscle weakness, loss of energy, and depression. Furthermore, hypogonadism also increases the risk of osteoporosis and is associated with the metabolic syndrome and cardiovascular disease (CVD). The hypothesized "Testicular Dysgenesis Syndrome" comprising low sperm counts, hypospadias, cryptorchidism, and finally TC, probably contributes to hypogonadism independent of applied TC treatment. Recently, an increased risk of accelerated hormonal ageing has been reported in TCSs in the very long term, i.e. 20 years after TC treatment.

Keywords: Hypogonadism; Testosterone; Infertility; Testicular cancer; Subfertility; Cryopreservation; Accelerated ageing

1. Introduction

Most patients with testicular cancer (TC) are cured and expected to live for decades after treatment [1]. Therefore, knowledge about long-term toxicities and long-term outcomes of hypogonadism and infertility or subfertility are particularly important for the group of testicular cancer survivors (TCSs) [2]. Hypogonadism and fertility issues are related to treatment intensity [3–5]. Testicular endocrine dysfunction, also called *hypoandrogenism*, comprises insufficient testosterone (T) production or compensatory increased luteinizing hormone (LH) levels. Inadequate spermatogenesis is measured by sperm counts, and as reflected by increased levels of follicle-stimulating hormone (FSH) and reduced fertility, which sometimes is the reason why some young males who contact the health care system for fertilization assistance, may ultimately receive the diagnosis of TC during the diagnostic work-up [6]. The incidence of TC among men has with abnormal results on semen analysis has been calculated to be 20 times higher than in the normal population [7].

This association is in concordance with the "testicular dysgenesis syndrome" (TDS), which has been hypothesized by Skakkebaek et al. [8], comprising low sperm counts, hypospadias, cryptorchidism, and finally TC. This group of researchers work in Denmark, a country where nearly 1% of men are diagnosed with TC, almost 1% of men have penile abnormalities at birth, and >40% of men have poor semen quality [9]. In addition to epidemiological evidence, histopathologic findings support the concept of TDS, which is thought to be related to fetal development complications [8]. Interestingly, maternal smoking during pregnancy has a stronger effect on spermatogenesis than a man's own smoking, also indicating that TDS symptoms that arise in adulthood may be already caused during fetal life [10].

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http://dx.doi.org/10.1016/j.urolonc.2015.01.014
1078-1439/

The group of Skakkebaek and Rajpert-De Meyts raised also concerns that not only TC incidence may have increased considerably during the recent years but also other components of the TDS, which may not be registered that reliably, such that TC may serve as a "whistleblower" of reproductive health problems [11].

Male hypogonadism is defined as a clinical syndrome that results from failure to produce physiological concentrations of T, normal amounts of sperm, or both [12], and may lead to reduced sexual functioning and well-being, fertility problems, muscle weakness, loss of energy, and depression [4,13,14]. Furthermore, hypogonadism also increases the risk of osteoporosis and is associated with the metabolic syndrome and cardiovascular disease [15–17]. In this article, an overview about fertility issues and hypogonadism has been provided, with a special focus on long-term hormonal ageing.

2. Physiology

The testicles have 2 major functions: generation of sperm cells and T (endocrine function). Hypothalamus-derived gonadotropin-releasing hormone are stimulated with oscillating levels production of LH and FSH in the anterior pituitary gland and their release to the blood stream.

Sperm cells (spermatozoa) are continuously produced by the testicular germinal epithelium, and the process from maturation of spermatogonias to mature sperm cells takes approximately 70 days. New cycles of spermatogenesis are initiated at regular time intervals (every 2–3 wk) before the previous ones are completed. FSH and T stimulate the Sertoli cells to provide hormonal and nutritional support for the spermatogenesis [18]. Regulated by FSH and spermatogenic status, Sertoli cells secrete Inhibin B, which limits FSH secretion through a negative feedback mechanism [19]. In adults, serum levels of Inhibin B correlate with total sperm count and testicular volume. Hence, both FSH and Inhibin B are useful markers of spermatogenesis. Spermatogenesis is usually evaluated by semen analyses, but in some cases, a testicular biopsy may be required.

T production is the principal testicular endocrine function and is prone to an age-related decrease [20]. T is mostly bound to circulating plasma proteins; 40% to 50% loosely bound to albumin and 50% to 60% tightly to sexual hormone–binding globuline, with only 1% to 2% representing free T. The latter and the albumin-bound T fraction form the effective pool determining the biological activity of T. As the amount of sexual hormone–binding globuline increases by age, the free serum T decreases in a more pronounced manner than the total T concentration [21].

3. Endocrine hypogonadism

T production is believed to be reduced already before TC diagnosis owing to the TDS [8]. TC treatment further affects the T production by the Leydig cells. Usually, the first sign of primary or testicular hypogonadism is an elevation of LH level to stimulate the Leydig cells. Firstly, when this stimulus is not sufficient, T levels start to decline. However, clinical symptoms such as loss of libido, anemia, fatigue, osteoporosis, and metabolic syndrome may, occur already when T production is compensated by increased LH. Alterations because of TDS might be subtle as Bandak et al. [22] found no significant differences in LH and T levels between controls and human choriogonadotropin negative–patients with unilateral stage I TC before orchiectomy. However, at 1 year after orchiectomy, a significant increase in LH level was observed. Elevated LH levels indicate critical Leydig cell capacity, as demonstrated by subsequently declining T level, rendering LH measurements clinically meaningful.

On the long term, several aspects contribute to hypogonadism and its deterioration over time in TCSs: the status of having only 1 testicle, TDS, TC treatment after orchiectomy, and finally ageing.

In unilaterally orchiectomized long-term survivors of testicular cancer TCSs, the prevalence of primary hypogonadism, as defined by LH levels >12 IU/l and/or testosterone <8 nmol/l, increases with treatment intensity [3]. After an observation time of median 11 years after treatment, TCSs had a 3.7-fold increased odds ratio (OR) for hypogonadism than age-matched males without TC did. Among TCSs, age greater than 45 years corresponded to a 1.4-fold increase in OR for hypogonadism. The corresponding ORs for TC treatment were 1.8 for surgery only, 3.6 for radiotherapy (RT), and 4.4 and 7.0 for cisplatin-based chemotherapy (CT) with cumulative cisplatin doses less than and greater than 850 mg, respectively.

Systemic CT does obviously affect testicular function, despite the so-called blood-testis barrier. This barrier refers to an intratubular nutritional germ cell compartment formed by the Sertoli cells. Blood vessels at that site are permeable such that cytostatic substances reach the intratubular cells, i.e., Leydig and Sertoli cells and spermatogonia. Consequently, sperm production is reduced after CT. However, as late-stage germ cells are less sensitive to cytotoxic treatment than early-stage germ cells are, it may take weeks until an effect on spermatogenesis is observable by sperm counts. Recovery of spermatogenesis relies on the ability of spermatogonial stem cells to survive drug toxicity and to retain the potential to differentiate to spermatocytes.

4. Accelerated hormonal ageing

An important question pertains to the further development of hypogonadism in long-term TCSs, which had been addressed by Sprauten et al. [5] in their publication "Longitudinal Serum Testosterone, Luteinizing Hormone, and Follicle-Stimulating Hormone Levels in a Population-Based Sample of Long-Term Testicular Cancer Survivors".