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ORIGINAL RESEARCH—EJACULATORY DISORDERS

Associations between Salivary Testosterone Levels, Androgen-Related Genetic Polymorphisms, and Self-Estimated Ejaculation Latency Time

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ABSTRACT

Introduction. Recently, testosterone (T) has been shown to be associated with premature ejaculation (PE) symptoms in the literature. Furthermore, studies suggest that the etiology of PE is partly under genetic control.
Aim. The aim of this study was to reassess findings suggesting an association between testosterone (T) and a key symptom of PE, ejaculation latency time (ELT), as well as exploratively investigating associations between six androgen-related genetic polymorphisms and ELT.
Materials and Methods. Statistical analyses were performed on a population-based sample of 1,429 Finnish men aged 18–45 years ($M = 26.9$, SD = 4.7). Genotype information was available for 1,345–1,429 of these (depending on the polymorphism), and salivary T samples were available from 384 men. Two androgen receptor gene-linked, two 5-alpha-reductase type 2-gene-linked, and two sex hormone-binding globuline gene-linked polymorphisms were genotyped.
Main Outcome Measures. Ejaculatory function was assessed using self-reported ELT.
Results. We found no association between salivary T levels and ELT. We found a nominally significant association between a 5-alpha-reductase type 2-gene-linked polymorphism (rs2208532) and ELT, but this association did not remain significant after correction for multiple testing. One single nucleotide polymorphism in the sex hormone-binding globulin gene (rs1799941) moderated (significantly after correction for multiple testing) the association between salivary T and ELT, so that A:A genotype carriers had significantly lower salivary T levels as a function of increasing ELT compared with other genotype groups.
Conclusions. We were unable to find support for the hypothesis suggesting an association between T levels and ELT, possibly because of the low number of phenotypically extreme cases (the sample used in the present study was population based). Our results concerning genetic associations should be interpreted with caution until replication studies have been conducted. **Jern P, Westberg L, Ankarberg-Lindgren C, Johansson A, Gunst A, Sandnabba NK, and Santtila P. Associations between salivary testosterone levels, androgen-related genetic polymorphisms, and self-estimated ejaculation latency time. Sex Med 2014;2:107–114.**

Key Words. ejaculation; testosterone; premature ejaculation; genetic; polymorphism; SNP; androgen

Introduction

Ejaculatory problems are common in the population, and problems relating to premature ejaculation (PE) are the most common male sexual complaints, with around 30% of men presenting subjective concerns regarding their ejaculatory function [1,2]. In the past two decades, increasingly ambitious efforts have been undertaken to elucidate the etiology of PE and the underlying mechanisms that trigger the ejaculatory reflex, but most of the variation in PE etiology remains poorly understood.

While it is well documented that sex steroids play a role in the regulation of most, if not all, aspects of male sexual behavior [3], the exact role of testosterone in the regulation of ejaculatory function is yet unclear. Studies conducted on animals have found no difference in plasma concentrations of T between sexually sluggish rats with intact and disrupted ejaculatory function [4]. Furthermore, sexually sluggish rats received no improvement in ejaculatory function when treated with subcutaneous T [5]. However, in humans, there is some evidence for direct T involvement in ejaculatory function, with indications of higher levels of both free and total T in PE patients [3,6,7]. In a study of 2,652 patients, including 674 with symptoms of PE and 194 with symptoms of delayed ejaculation (DE), significant effects of small effect size were observed indicating elevated T levels in PE patients, and decreased T levels in DE patients [6]. This effect appeared as a linear function of severity of ejaculatory problems, so that individuals with the most severe PE problems also displayed the highest T values, and individuals with the most severe DE problems displayed the lowest T levels. In addition, Corona and his associates [7] noted similar effects of thyrotropin and prolactin, but in the opposite direction (e.g., so that high levels of these were associated with more severe DE symptoms). In addition, in a study of men in couples with infertility, levels of free T were found to be positively associated with elevated PE scores [8]. In summary, results from empirical studies regarding the role of T in ejaculatory function are inconclusive.

It is conceivable that sex steroid-related genetic polymorphisms could influence ejaculatory function in men in two ways: directly (i.e., exert a main effect on either T levels or ejaculatory function) or indirectly through moderation of the association between, for example, T and ejaculatory function. Of the androgen-related genetic polymorphisms, the CAG repeat polymorphism in the androgen receptor gene (*arCAG*) has been extensively studied in other contexts. Furthermore, the *arCAG* polymorphism has been shown to moderate the association between T and various phenotypes and conditions, for example, andropausal symptoms [9], symptoms of mood disorders [10,11], and insulin sensitivity [12]. However, other genes could also conceivably play a direct or indirect role in the regulation of ejaculatory function. Functional polymorphisms in gene coding for 5-alpha-reductase type 2 (SRD5A2), a substance that processes T into the more potent dihydrotestosterone (DHT), and sex hormone-binding globulin (SHBG), which binds and inhibits the function of sex hormones (particularly T and DHT), are of particular interest given their central role in sex hormone regulation. For example, *SHBG* gene polymorphisms have been shown to independently predict levels of both free (rs6259) and total T (rs1799941) at least in aging men [13]. Recently, *SRD5A2* polymorphisms were also shown to influence semen quality [14].

In the present study, we attempted to establish empirical support for the hypothesis of T involvement in the regulation of ejaculatory function in humans. Based on previous empirical findings [7], we expected levels of salivary T to be associated with shorter ejaculation latency time (ELT). In order to elucidate potential agents that could moderate the association between T and ELT, and based on findings in the literature, we decided to investigate whether a total of six sex steroid-related functional genetic polymorphisms (two androgen receptor gene-related, two 5-alpha-reductase gene-related [*SRD5A2*], and two sex hormone-binding globulin [*SHBG*] gene-related) had such interactive effects with T on ELT. We also wanted to investigate whether any of these polymorphisms had a direct main effect on ELT.

Materials and Methods

Participants

In the present study, we started out using a sample of 3,331 male twin individuals and brothers of twins, who had participated in the Genetics of Sexuality and Aggression study, a population-based study of Finnish twins and siblings of twins stemming from a data collection carried out in 2006. The overall response rate for this data collection was 45%. Data were collected through two channels: postal mail and a secure, online questionnaire (participants were free to choose between these two options). Individuals who had