Influence of Androgen Receptor CAG Polymorphism on Sexual Function Recovery after Testosterone Therapy in Late-Onset Hypogonadism

Giacomo Tirabassi, MD,* Giovanni Corona, MD,†‡ Andrea Biagioli, MD,* Eddi Buldreghini, PhD,* Nicola delli Muti, PhD,* Mario Maggi MD,‡ and Giancarlo Balercia, MD*

*Andrology Unit, Division of Endocrinology, Department of Clinical and Molecular Sciences, Polytechnic University of Marche, Ancona, Italy; †Endocrinology Unit, Maggiore-Bellaria Hospital, Bologna, Italy; ‡Andrology Unit, Department of Clinical Physiopathology, University of Florence, Florence, Italy

DOI: 10.1111/jsm.12790

ABSTRACT

Introduction. Androgen receptor (AR) CAG polymorphism has been found to influence sexual function. However, no study has evaluated its potential to condition sexual function recovery after testosterone replacement therapy (TRT) in a large cohort of hypogonadic subjects.

Aim. To evaluate the role of this polymorphism in sexual function improvement after TRT in late-onset hypogonadism (LOH).

Methods. Seventy-three men affected by LOH were retrospectively considered. Evaluations were performed before TRT started (time 0) and before the sixth undecanoate testosterone injection.

Main Outcome Measures. International Index of Erectile Function (IIEF) questionnaire (erectile function [EF], orgasmic function [OF], sexual desire [SD], intercourse satisfaction [IS], overall satisfaction [OS], and total IIEF-15 score); total and free testosterone and estradiol; AR gene CAG repeat number.

Results. TRT induced a significant increase in total and free testosterone and estradiol. All IIEF domains significantly improved after TRT. AR CAG repeats negatively and significantly correlated with all the variations (Δ-) of sexual function domains, except for Δ-OS. Conversely, Δ-total testosterone was found to be positively and significantly correlated with sexual function domain variations, except for Δ-IS and Δ-OS. Δ-estradiol did not correlate significantly with any of the variations of sexual function domains. After inclusion in generalized linear models, the number of AR gene CAG triplets was found to be independently and negatively associated with Δ-EF, Δ-SD, Δ-IS, and Δ-Total IIEF-15 score, whereas Δ-total testosterone was independently and positively associated with Δ-EF, Δ-OF, Δ-SD, and Δ-Total IIEF-15 score. However, after including time 0 total testosterone in the model, AR gene CAG triplets remained independently and negatively associated only with Δ-EF and Δ-Total IIEF-15 score, whereas Δ-total testosterone was independently and positively associated only with Δ-EF.

Conclusions. Longer length of AR gene CAG repeat tract seems to lower TRT-induced improvement of sexual function in LOH. **Tirabassi G, Corona G, Biagioli A, Buldreghini E, delli Muti N, Maggi M, and Balercia G. Influence of androgen receptor CAG polymorphism on sexual function recovery after testosterone therapy in late-onset hypogonadism. J Sex Med 2015;12:381–388.**

Key Words. Androgen Receptor; Late-Onset Hypogonadism; Sexual Function; International Index of Erectile Function Questionnaire; Testosterone Replacement Therapy

Introduction

Androgen receptor (AR) CAG polymorphism is a widely studied genetic parameter that is becoming increasingly important in the andrology field [1,2]. AR is a protein containing a central DNA binding domain, a ligand binding domain at the carboxy-terminal extremity and an aminoacid sequence of variable length at the amino-terminal extremity, important for the full transcriptional activity of the receptor [3]. The latter region is codified by exon 1 of the AR gene (chromosome X, q11-q12) containing a varying number of CAG triplets, which encode for a polyglutamine tract [3]. The number of CAG repeats ranges from about 10 to 35 with a mean of 21–23 in normal men [4].

AR CAG polymorphism seems to influence testosterone action. In fact, although a certain inconsistency exists on this issue, longer CAG repeats have generally been found to be associated with decreased transcriptional activity of the receptor, resulting in lower hormonal effects on several target tissues (e.g., bone, body composition, lipid and glycemic profile) [5–8]. In this regard, subjects affected by Kennedy Syndrome present a number of CAG repeats greater than 40 together with decreased virilization, testicular atrophy, reduced sperm production, and infertility [8]. However, a relatively low number of reports have focused on the relationship between AR CAG polymorphism and sexual function [3,9–12]. Among these studies, only one has dealt with the role of AR CAG polymorphism in influencing sexual improvement after testosterone replacement therapy (TRT); however, that article focused on a particular and rare form of hypogonadism, i.e., post-surgical hypogonadotropic hypogonadism [3].

Aims

In this article we aimed at evaluating the role of CAG repeat polymorphism in conditioning the recovery of sexual function in a large cohort of subjects affected by late-onset hypogonadism and undergoing TRT.

Methods

Subjects

Registration of patients who attended our andrology unit from 2003 to present was retrospectively reviewed, and 73 men were studied. Selection criteria were: (i) diagnosis of late-onset hypogonadism, based on unequivocally low levels of serum testosterone (total testosterone < 2.31 ng/mL or, in case of total testosterone between 2.31 and 3.46 ng/mL, calculated free testosterone < 65 pg/mL) together with signs and symptoms consistent with hypogonadism [13,14]; (ii) sexual relationship for at least 1 year before enrolment and continued during the study period; (iii) data availability for the duration of analysis; (iv) absence of previous investigation or treatment for sexual dysfunction. Exclusion criteria were: (i) neoplastic disorders; (ii) endocrine disorders other than type 2 diabetes mellitus; (iii) alcohol or drug dependence; (iv) male-gender-specific disorder (e.g., benign hypertrophy of prostate, chronic prostatitis, urinary incontinence); and (v) mental illness.

Study Protocol

Subjects were considered before TRT started (time 0) and before the sixth undecanoate testosterone injection (50–60 weeks after the first testosterone injection) (recovery phase); clinical, biochemical, and sexual evaluations performed at the two time points were considered in the analysis. Undecanoate testosterone (1,000 mg intramuscularly) was administered by giving a second injection 6 weeks after the first (loading dose) and then continuing with similar injections after 10–14 weeks depending on blood testosterone levels and clinical symptoms [15].

Clinical, biochemical, and sexual data were collected as part of the routine clinical procedure of this retrospective study. Genetic analysis was performed as part of a previous prospective research protocol, started in 2003, which evaluated AR CAG polymorphism in patients followed by our unit affected by hypogonadism and infertility. Institutional review board approval was obtained, and all patients gave informed consent. The study was performed according to the Declaration of Helsinki.

Main Outcome Measures

Sexual Assessment

The International Index of Erectile Function-15 questionnaire (IIEF-15) [16] was administered to patients. This questionnaire considers five aspects of male sexual life: erectile function (EF), orgasmic function (OF), sexual desire (SD), intercourse