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

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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.


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...
satisfaction (IS), and overall satisfaction (OS). EF (items 1, 2, 3, 4, 5, and 15), OF (items 9 and 10), SD (items 11 and 12), IS (items 6, 7, and 8), and OS (items 13 and 14) domains were used to assess the effect of TRT. According to this score, EF can be normal (score range 26–30), slightly impaired (score range 17–25), moderately impaired (score range 11–16), or severely impaired (score less than 11). As far as OF (score range 0–10), SD (score range 2–10), IS (score range 0–15), and OS (score range 2–10) are concerned, the higher the score the better is the parameter studied. Total IIEF-15 score was also taken into account.

**Hormone Evaluation**

The following biochemical and hormone parameters were considered: follicle-stimulating hormone (FSH), luteinizing hormone (LH), total testosterone, estradiol, sex hormone-binding globulin (SHBG). All hormone assays were carried out using immunoassay commercial kits. The normal male reference ranges for the parameters studied were the following: FSH, 1.7–6.9 IU/L; LH, 1.6–10.0 IU/L; total testosterone, 3–8.5 ng/mL; estradiol, 11–47 pg/mL; SHBG, 20–60 nmol/L. Free testosterone was calculated according to Vermeulen’s formula (at http://www.issam.ch/freetesto.htm) [17].

**Polymerase Chain Reaction (PCR) Amplification and Sequencing**

CAG polymorphism of the AR gene in exon 1 (GenBank: M35844.1) was identified using PCR and sequencing analysis. Genomic DNA (150 ng) was amplified by PCR in a reaction containing 10 pmol/μL of each of the primers (Invitrogen, Paisley, UK) (A0) sense 5′- GTG-GTT-GCT-CCC-GCA-AGT-TTC-C-3’ and (A2) antisense 5′- GCT-GTG-AAG-GTT-GCT-GTT-CCTC-3’ [4]. A 3% concentration of dimethylsulfoxide was added to improve yield and specificity. Final reaction was performed with the Dynazyme DNA polymerase (Finnzymes Oy, Espoo, Finland). PCR reaction was performed under the following conditions: 98°C for 1 minute, 68°C for 1 minute, 72°C for 1 minute, repeated 37 times. After incubation at 98°C for 1 minute, reactions were cycled for 10” at 98°C, 15° 68°C, and 15° at 72°C for 35 cycles, followed by a final extension for 7 minutes at 72°C. After purification, PCR products were sequenced on a Beckman Coulter CEQ 2000XL with the primer A2.

**Statistical Analysis**

Shapiro–Wilk’s test was applied to verify the normal distribution of the continuous variables, which are expressed as median (interquartile range) when not-normally distributed, and as mean ± standard error of the mean when normally distributed. Categorical variables are expressed as frequencies. Variations of anthropometric, hormone and sexual parameters between the two phases (Δ-) were calculated as the value present at the recovery phase minus the value present at time 0; statistical comparison between the two phases was made using Student’s t-test for paired data or Wilcoxon’s test depending respectively on normal or not normal data distribution. Comparisons between two groups were performed with unpaired Student’s t-test or Mann–Whitney’s U-test in case of normal or not normal data, respectively.

Biologically important hormones, which significantly varied after TRT, and genetic parameters, were involved in correlation analysis using bivariate Spearman correlations.

Generalized linear models were used to determine the associations between the parameters of sexual function with the variables that were significantly correlated in the previous analysis. Sexual parameters were used individually as dependent variables, while the number of AR gene CAG triplets and Δ-total testosterone were the covariates.

In order to assess the influence of time 0 total testosterone as a possible confounding factor, this same analysis was repeated including also that variable as covariate in each model. Decision tree analysis (CHAID algorithm) was used to identify subgroups of patients with different response to testosterone therapy (dependent variable) by the number of CAG triplets (independent variable). As regards the rules, a minimum parental node size of 70 subjects, a minimum child node size of 20 subjects and a α level of 0.05 for both splitting nodes and merging categories were used.

Significance was set at P < 0.05. Statistical analyses were performed using SPSS 16 package (SPSS Inc., Chicago, IL, USA).

**Results**

Figure 1 shows the frequency of the number of AR CAG repeats in our sample (median: 19; total range 12–25). Table 1 shows the general, anthropometric and hormone characteristics of studied subjects. As expected, TRT induced a significant decrease in FSH and LH values, while total and
free testosterone and estradiol significantly increased (Table 1). No significant changes were evident in body mass index (BMI) and SHBG levels (Table 1).

Sexual function clearly and significantly improved in all the IIEF domains (Table 2).

AR CAG repeats negatively and significantly correlated with all the variations of sexual function domains except for $\Delta$-OS (Table 3). Conversely, $\Delta$-total testosterone was found to be positively and significantly correlated with sexual function domain variations except for $\Delta$-IS and $\Delta$-OS (Table 3). $\Delta$-estradiol did not correlate significantly with any of the variations of sexual function domains (Table 3). Subjects with and without type 2 diabetes mellitus or cardiovascular diseases did not significantly differ in AR gene CAG length, $\Delta$-total testosterone, $\Delta$-EF, $\Delta$-OF, $\Delta$-SD, $\Delta$-IS, $\Delta$-OS, and $\Delta$-Total IIEF-15 score testifying that these clinical conditions were not confounding variables in the context of our analysis (data not shown).

### Table 1 General, anthropometric, and hormone characteristics of studied subjects

<table>
<thead>
<tr>
<th>General characteristics</th>
<th>Time 0</th>
<th>Recovery phase</th>
<th>$\Delta$</th>
<th>$P^1$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>General characteristics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>60.04 ± 0.45</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of AR gene CAG triplets</td>
<td>19 (15–21)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type 2 diabetes mellitus (yes/no)</td>
<td>20/53</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular diseases (yes/no)</td>
<td>25/48</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Anthropometric and hormone characteristics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>28.1 ± 0.36</td>
<td>28.2 ± 0.33</td>
<td>0.17 ± 0.15</td>
<td>NS</td>
</tr>
<tr>
<td>FSH (IU/L)</td>
<td>15.2 (13.1–19.5)</td>
<td>6.4 (3.7–10.4)</td>
<td>$-9.2$ ($-13.3$–$-5.2$)</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>LH (IU/L)</td>
<td>12.8 (12–13.4)</td>
<td>3.5 (2.1–4.8)</td>
<td>$-9.3$ ($-11$–$-7.5$)</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>Total testosterone (ng/mL)</td>
<td>2.08 (1.69–2.77)</td>
<td>3.80 (3.51–4.10)</td>
<td>1.61 (1.35–1.96)</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>Free testosterone (pg/mL)</td>
<td>40.7 (33.6–55.3)</td>
<td>82.1 (75.7–90.3)</td>
<td>39.8 (32.3–46.6)</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>Estradiol (pg/mL)</td>
<td>7 (5.2–8.3)</td>
<td>28.6 (20.9–35.4)</td>
<td>21.1 (14–27.7)</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>SHBG (nmol/L)</td>
<td>30.4 (26.1–33.7)</td>
<td>29.5 (27–31.2)</td>
<td>$-2$ ($-4.3$–$-3.3$)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Continuous variables are expressed as median (interquartile range) or mean ± standard error of the mean. Categorical variables are expressed as frequencies.

$^1$Statistical comparison between time 0 and recovery phase.

$\Delta$ = variation; AR = androgen receptor; BMI = body mass index; FSH = follicle-stimulating hormone; LH = luteinizing hormone; SHBG = sex hormone-binding globulin; NS = not significant.
After inclusion in generalized linear models, 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 (Table 4).

However, after including in that same model also time 0 total testosterone as covariate, the number of AR gene CAG triplets remained independently and negatively associated only with Δ-EF and Δ-Total IIEF-15 score (Table 4). On the other hand, Δ-total testosterone was independently and positively associated only with Δ-EF (Table 4).

Decision tree analysis defined two groups of patients having a different variation of Total IIEF-15 score after the therapy, by the number of AR CAG triplets ($P < 0.001$). Indeed, comparison of the two groups by Mann–Whitney’s $U$-test showed that the subjects with a number of AR CAG triplets below or equal to 20 had a higher Δ-Total IIEF-15 score (median = 31.5; interquartile range = 28–33) compared with those with a number of AR CAG triplets above 20.

### Table 2  Sexual parameters before and after TRT

<table>
<thead>
<tr>
<th></th>
<th>Time 0</th>
<th>Recovery phase</th>
<th>Δ</th>
<th>$P^1$</th>
</tr>
</thead>
<tbody>
<tr>
<td>EF</td>
<td>14 (9–18)</td>
<td>25 (22–28.5)</td>
<td>11 (10–13)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>OF</td>
<td>6 (4–7)</td>
<td>9 (8.5–10)</td>
<td>3 (3–4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SD</td>
<td>6 (4–7)</td>
<td>8 (8–9)</td>
<td>2 (2–4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>IS</td>
<td>7 (6–8)</td>
<td>14 (13–14)</td>
<td>6 (6–7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>OS</td>
<td>4 (3–4)</td>
<td>9 (8.5–10)</td>
<td>5 (5–6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total IIEF-15 score</td>
<td>36 (28.5–44)</td>
<td>65 (60–71.5)</td>
<td>28 (27–33)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Values are expressed as median (interquartile range).

$^1$Statistical comparison between time 0 and recovery phase.

TRT = testosterone replacement therapy; Δ = variation; EF = erectile function; OF = orgasmic function; SD = sexual desire; IS = intercourse satisfaction; OS = overall satisfaction; IIEF-15 = International Index of Erectile Function

### Table 3  Spearman correlations between hormone and genetic parameters and sexual function in the whole sample

<table>
<thead>
<tr>
<th></th>
<th>Δ-EF</th>
<th>Δ-OF</th>
<th>Δ-SD</th>
<th>Δ-IS</th>
<th>Δ-OS</th>
<th>Δ-Total IIEF-15 score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of AR gene CAG triplets</td>
<td>r: −0.699</td>
<td>r: −0.399</td>
<td>r: −0.546</td>
<td>r: −0.293</td>
<td>NS</td>
<td>r: −0.675</td>
</tr>
<tr>
<td></td>
<td>$P &lt; 0.001$</td>
<td>$P &lt; 0.001$</td>
<td>$P &lt; 0.001$</td>
<td>$P &lt; 0.012$</td>
<td></td>
<td>$P &lt; 0.001$</td>
</tr>
<tr>
<td>Δ-total testosterone</td>
<td>r: 0.688</td>
<td>r: 0.476</td>
<td>r: 0.612</td>
<td>NS</td>
<td>NS</td>
<td>r: 0.630</td>
</tr>
<tr>
<td></td>
<td>$P &lt; 0.001$</td>
<td>$P &lt; 0.001$</td>
<td>$P &lt; 0.001$</td>
<td></td>
<td></td>
<td>$P &lt; 0.001$</td>
</tr>
<tr>
<td>Δ-estradiol</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

Δ = variation; EF = erectile function; OF = orgasmic function; SD = sexual desire; IS = intercourse satisfaction; OS = overall satisfaction; IIEF-15 = International Index of Erectile Function; AR = androgen receptor; NS = not significant

### Table 4  Generalized linear models evaluating the influence of number of AR gene CAG triplets and Δ-total testosterone on sexual function

<table>
<thead>
<tr>
<th></th>
<th>Δ-EF</th>
<th>Δ-OF</th>
<th>Δ-SD</th>
<th>Δ-IS</th>
<th>Δ-Total IIEF-15 score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1</td>
<td>β</td>
<td>$P$ value</td>
<td>β</td>
<td>$P$ value</td>
<td>β</td>
</tr>
<tr>
<td>Number of AR gene CAG triplets</td>
<td>−0.273</td>
<td>&lt;0.001</td>
<td>−0.039</td>
<td>NS</td>
<td>−0.100</td>
</tr>
<tr>
<td>Δ-total testosterone</td>
<td>1.502</td>
<td>&lt;0.001</td>
<td>0.494</td>
<td>0.017</td>
<td>0.832</td>
</tr>
<tr>
<td></td>
<td>0.054</td>
<td>0.018</td>
<td>0.048</td>
<td>NS</td>
<td>3.119</td>
</tr>
<tr>
<td></td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 2</td>
<td>β</td>
<td>$P$ value</td>
<td>β</td>
<td>$P$ value</td>
<td>β</td>
</tr>
<tr>
<td>Number of AR gene CAG triplets</td>
<td>−0.174</td>
<td>&lt;0.001</td>
<td>0.009</td>
<td>NS</td>
<td>−0.038</td>
</tr>
<tr>
<td>Δ-total testosterone</td>
<td>0.902</td>
<td>0.015</td>
<td>0.043</td>
<td>NS</td>
<td>0.312</td>
</tr>
<tr>
<td></td>
<td>−0.043</td>
<td>NS</td>
<td>−0.270</td>
<td>0.002</td>
<td>1.231</td>
</tr>
</tbody>
</table>

$^1$Statistical comparison between time 0 and recovery phase.

TRT = testosterone replacement therapy; Δ = variation; EF = erectile function; OF = orgasmic function; SD = sexual desire; IS = intercourse satisfaction; IIEF-15 = International Index of Erectile Function; AR = androgen receptor; NS = not significant

Data are from separate generalized linear models. $P$ values assessed using Wald chi-square test for regression coefficient. Model 1 included sexual parameters, used individually, as dependent variables, and the number of AR gene CAG triplets and Δ-total testosterone as covariates. Model 2 included sexual parameters, used individually, as dependent variables, and the number of AR gene CAG triplets, Δ-total testosterone and time 0 total testosterone as covariates.
20 (median = 26; interquartile range = 25–27) (P < 0.001).

Discussion

The involvement of AR in male sexual function is suggested by several findings. First, both in man and in rat, testosterone receptors were found in cavernous tissues throughout life, with higher levels during pubertal phase when penis growth occurs; however, as rats age, androgen-binding activity declines [18]. Second, several studies, prevalently conducted on animals, established AR expression in hypothalamus, temporal, prefrontal and cingulate cortex, amygdala, mammillary nuclei, and diagonal band of Broca, suggesting its involvement in human sexual arousal [19]. The limited evidence of AR distribution in humans derives from studies of the temporal cortex, which found substantial amounts of AR protein [19]. Moreover, in partial androgen insensitivity syndrome a moderate or severe decrease of EF, OF, SD, IS, and OS is evident [20]; also, penile length averages 40.6 (mean) ± 6 (standard deviation) mm, less than 5 standard deviation values of the normal mean of Caucasian males, i.e., 133 ± 16 mm [20].

The present study is the first one to assess, in a large number of subjects affected by late-onset hypogonadism, the role of CAG repeat polymorphism in TRT-induced recovery of sexual function. We found that the improvements in EF, SD, IS, and total IIEF-15 score were independently and negatively influenced by the longer length CAG repeat polymorphism (Table 4). However, we also evaluated these associations after adjusting for time 0 total testosterone, as literature data show that sexual function improvement after TRT depends on baseline testosterone levels [21–24]. We found that only the associations of short CAG repeat tracts with Δ-EF and Δ-total IIEF-15 score remained significant (Table 4). On the other hand, as far as testosterone influence on sexual function is concerned, in our sample, total testosterone increase was found to independently and favourably condition EF, OF, SD, and Δ-total IIEF-15 recovery (Table 4). However, after adjustment for baseline total testosterone levels, only the associations with Δ-EF remained significant (Table 4). In addition, our analysis revealed that a lower response to TRT occurred in CAG repeat values of over 20.

These results confirm the ones obtained by the only other study that has dealt with this issue [3]. In fact, in that work, patients affected by postsurgical hypogonadotropic hypogonadism were evaluated, and CAG repeat length was found to be negatively associated with TRT-related improvement of EF, SD, IS, OS, and IIEF-15 total score [3], independently of the well-known sexual effects of pituitary replacement therapies [16,25–32]. Some discrepancies in the results between that study and the present one could be due to certain differences in the methodological aspects and sample characteristics. First, in that report, a particular and rare form of hypogonadism, i.e., postsurgical hypogonadotropic hypogonadism, was considered, and fifteen subjects were included in that protocol [3]. Also, duration of hypogonadism in that work was relatively short (mean 8.46 months; standard deviation 1.88) [3]. Moreover, younger mean age (mean 55 years; standard deviation 8.64) and a later recovery phase timepoint (before the eighth testosterone injection, 74–84 weeks after the first) [3] might have contributed to the different results.

In cross-sectional studies, a greater discrepancy on this issue, probably due to lack of homogeneity in recruited sample (e.g., age) and methodological procedures, emerges. In fact, in the abstract by Pastuszak et al., who considered the medical records of 85 men (mean age and standard deviation: 50.7 ± 14.7 years) presenting to their clinic, AR gene CAG repeat number was inversely correlated with all aspects of male sexual function assessable by IIEF-15 [10], therefore agreeing, to some extent, with our findings. Similarly, Liu et al., by conducting a free health screening in men older than 40 years (mean age and standard deviation: 57.2 ± 6.5 years), found that, when total testosterone levels were above 3.40 ng/mL, subjects with AR CAG repeat lengths ≥ 25 had a significantly higher risk of developing andropausal symptoms (ADAM questionnaire) than those with AR CAG repeat lengths ≤ 22, but this was not observed when total testosterone levels were equal or less than 3.40 ng/mL [12]. On the contrary, Andersen et al., who evaluated 79 men with erectile dysfunction complaints (mean age and standard deviation 52.7 ± 16 years) and 340 controls in a population-based survey, found no associations between erectile dysfunction symptomatology and CAG repeat length [9]. Of note, these authors used a single question taken from the National Institutes of Health Consensus Development Panel on Impotence [33] to evaluate ED complaints [9]. Finally, Härkönen et al., in 213 41–70-year-old men randomly selected from the
Population Registry, reported that the CAG repeat number was positively correlated with depression, as expressed by the desire to be dead and by a depressed mood, whereas men with CAG repeats greater or equal to 23 reported decreased potency (Heinemann questionnaire) less often than the others [11].

It is also worth noting that recovery of EF after TRT has great inter-individual variability. As demonstrated by an important meta-analysis, this depends mainly on the initial levels of testosterone as greater effects have been noticed in severely hypogonadal men (total testosterone < 2.02 ng/mL), and in those with partial androgen decline (total testosterone > 2.02 but >3.46 ng/mL) [21]. On the contrary, the effects of testosterone in studies with basal testosterone above 3.46 ng/mL were much smaller or not significant [21]. However, a certain degree of variability in EF recovery was evident even in subjects with low baseline levels of testosterone [21]. In view of our results, CAG polymorphism may exert a modulatory effect on sexual improvement and could represent one of the parameters able to justify this variable response to TRT.

In conclusion, our work has demonstrated for the first time the increased TRT-induced improvement of sexual symptoms in late-onset hypogonadism patients with longer length of AR gene CAG repeat number. If our data will be further confirmed, the evaluation of this genetic parameter could lead to pharmacogenetically select the optimal TRT dose in hypogonadal subjects [34].

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Statement of Authorship

Category 1

(a) Conception and Design
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Giacomo Tirabassi; Nicola delli Muti; Eddi Buldrehagini; Andrea Biagioli

(c) Analysis and Interpretation of Data
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Category 2

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References


