SEXUAL MEDICINE ORIGINAL RESEARCH

Androgen Receptor CAG Repeat Length as a Risk Factor of Late-Onset Hypogonadism in a Korean Male Population

Jong Wook Kim, MD, PhD,[1,2] Young Dae Bae, MD,[1,2] Sun Tae Ahn, MD,[1,2] Jin Wook Kim, MD, PhD,[2,3] Je Jong Kim, MD, PhD,[1,2] and Du Geon Moon, MD, PhD[1,2]

ABSTRACT

Background: Testosterone action is mediated through the androgen receptor (AR), whose sensitivity is influenced by the AR CAG repeat polymorphism. However, the relation between late-onset hypogonadism (LOH) and AR CAG repeat length is unclear and studies of Asian populations are limited.

Aim: To investigate the relation between AR CAG repeat length and LOH in Korean men.

Methods: 263 Korean men (mean age = 63.43 ± 10.9 years) were enrolled from 2014 to 2015. LOH diagnosis was based on a serum testosterone level lower than 3.5 ng/mL and positive androgen deficiency according to the Aging Males' Symptom Scale (AMS). Total testosterone levels and answers to the LOH-related questionnaire were analyzed.

Outcomes: The relation between AR CAG repeat length and LOH was determined.

Results: Mean CAG repeat length was 22.1 ± 4.6 and mean serum testosterone levels were 2.6 ± 0.7 and 6.0 ± 2.0 ng/mL in men with and without LOH, respectively. Men with LOH showed significantly longer AR CAG repeat lengths than men without LOH (26.1 vs 21.6, $P < .001$). Longer CAG repeat lengths were correlated with higher AMS total scores (r = 0.454, $P = .001$) and AMS psychotic, somatic, and sexual subscores (r = 0.276, 0.246, and 0.571, $P = .006$, .007, .001, respectively) and significantly lower 5-item International Index of Erectile Function scores (r = −0.261, $P = .001$). Multivariate analysis showed that patient age and CAG repeat length were independently associated with LOH (odds ratio = 1.05 and 1.29, $P = .041$ and <.001, respectively).

Clinical Implications: A longer CAG repeat length is associated with LOH symptoms and LOH.

Strengths and Limitations: Associations between CAG repeats and LOH were verified in Korean patients. Moreover, a longer CAG repeat length was shown to be an independent risk factor for LOH. Limitations included the small number of LOH patients studied and that other sex hormone-associated factors were not measured.

Conclusions: AR CAG repeat length was associated with LOH prevalence and clinical symptoms in this Korean male population. Thus, it is important to measure CAG repeat length for patients with LOH symptoms with normal testosterone levels. **Kim JW, Bae YD, Ahn ST, et al. Androgen Receptor CAG Repeat Length as a Risk Factor of Late-Onset Hypogonadism in a Korean Male Population. Sex Med 2018;X:XXX−XXX.**

Key Words: Androgen Receptor; CAG Repeat; Late-Onset Hypogonadism; Testosterone

INTRODUCTION

Late-onset hypogonadism (LOH) or testosterone deficiency syndrome, a clinical and biochemical syndrome characterized by typical symptoms and a deficiency in serum testosterone, can adversely affect multiple organ functions and quality of life.[1−3] LOH is diagnosed by testosterone measurement and symptom questionnaires; however, these methods have limitations.

Received November 23, 2017. Accepted April 1, 2018.

[1]Department of Urology, Korea University College of Medicine, Seoul, Korea;

[2]Institute of Regenerative Medicine, Korea University, Seoul, Korea;

[3]Department of Urology, Chung-Ang University College of Medicine, Seoul, Korea

https://doi.org/10.1016/j.esxm.2018.04.002

Table 1. Comparison of demographic characteristics and laboratory data between men with LOH and those without LOH

	All (N = 262)	LOH(−) (n = 229)	LOH(+) (n = 33)	*P* value
Age (y)	63.5 ± 7.4	63.0 ± 7.4	66.1 ± 7.7	.024*
CAG repeat length	22.1 ± 4.6	21.5 ± 4.4	26.1 ± 4.0	<.001*
Total testosterone (ng/mL)	5.6 ± 2.2	6.0 ± 2.0	2.6 ± 0.7	<.001*
IPSS total score	14.0 ± 7.8	13.9 ± 7.7	14.0 ± 8.2	.949
IPSS voiding score	8.2 ± 5.2	8.1 ± 5.2	8.2 ± 5.2	.915
IPSS storage score	5.6 ± 3.5	5.6 ± 3.4	5.6 ± 3.8	.956
IPSS QOL score	3.5 ± 1.2	3.5 ± 1.2	3.7 ± 1.3	.266
AMS total score	34.5 ± 11.4	34.0 ± 11.5	38.4 ± 10.2	.038*
AMS psychological score	8.1 ± 3.2	8.0 ± 3.3	8.6 ± 2.3	.294
AMS somato-vegetative score	13.9 ± 4.8	14.0 ± 4.9	13.8 ± 4.2	.826
AMS sexual factor score	12.5 ± 5.5	12.0 ± 5.3	16.0 ± 5.6	<.001*
IIEF-5 total score	11.6 ± 7.3	11.9 ± 7.3	9.7 ± 7.0	.102
PHQ total score	3.1 ± 3.9	3.17 ± 4.1	2.9 ± 2.9	.690

AMS = Aging Males' Symptom Scale; IIEF-5 = 5-item International Index of Erectile Function; IPSS = International Prostate Symptom Score; LOH = late-onset hypogonadism; PHQ = Patient Health Questionnaire–9; QOL = quality of life.
*$P < .05$.

Although symptom questionnaires such as the Androgen Deficiency in Aging Males (ADAM) questionnaire,[4] the Aging Males' Symptom Scale (AMS),[5] the Massachusetts Male Aging Study questionnaire (MMAS), the New England Research Institute Hypogonadism Screener, and the ANDROTEST are universally applied, they exhibit low specificity.[6] Morley et al[7] reported sensitivities of 97% for the ADAM questionnaire, 83% for the AMS, and 60% for the MMAS questionnaire. Specificities were only 30% for the ADAM questionnaire, 39% for the AMS, and 59% for the MMAS questionnaire.

Moreover, some investigators reported that total, free, and bioavailable testosterone levels do not correlate with the clinical symptoms of LOH.[8,9] In addition, testosterone is characterized by diurnal and yearly variations, resulting in differentiations in its measurements for the same person depending on the time of measurement. Because of their inaccuracies in testosterone measurements and questionnaire answers, LOH is not easily diagnosed, limiting effective treatment.

The effect of testosterone is mediated through the androgen receptor (AR), the gene for which is located on Xq11-12 and contains 8 exons.[10] The AR gene contains a repeated nucleotide sequence region, [CAG]nCAA (known as the CAG repeat polymorphism and denoted as [CAG]n), which codes for a polyglutamine tract in the N-terminal transactivation domain of exon 1.[11]

The repeat length of CAG is negatively correlated with the transcriptional activity of target genes and can modulate AR activity.[12] The length of the CAG repeat sequence spans 9 to 36 repeats, with an average length of 21 repeats in Caucasian populations.[13] However, there are significant ethnic variations in the allelic distribution of the AR CAG repeat.[13,14] Although [CAG]n appears to be associated with LOH or testosterone deficiency, the number of studies of [CAG]n in Asian male populations is very limited.

We explored the relation between AR [CAG]n and serum testosterone levels and LOH in a Korean male population.

METHODS

Subjects

The study protocol was reviewed and approved by the institutional review board of Korea University Guro Hospital (Seoul, Korea).

A cross-sectional study was carried out at the university hospital from June 2014 to May 2015. The inclusion criterion was men older than 40 years who were recruited from an LOH

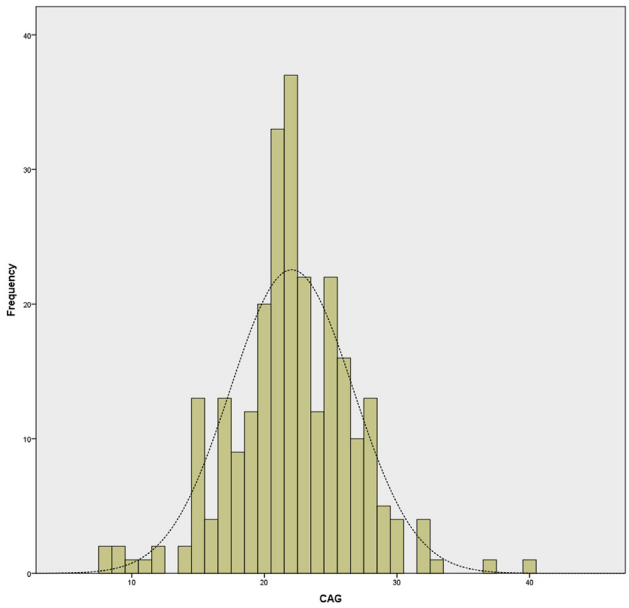

Figure 1. Distribution of the number of androgen receptor CAG repeats in the study population. AMS = Aging Males' Symptom Scale.