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Effects of 8-Year Treatment of Long-Acting Testosterone Undecanoate on Metabolic Parameters, Urinary Symptoms, Bone Mineral Density, and Sexual Function in Men With Late-Onset Hypogonadism

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ABSTRACT

Introduction: The long-term effects of long-acting testosterone undecanoate (TU) and androgen receptor CAG repeat lengths in Thai men with late-onset hypogonadism (LOH) have not been reported.

Aim: To analyze the 8-year follow-up effects of intramuscular TU therapy on metabolic parameters, urinary symptoms, bone mineral density, and sexual function and investigate CAG repeat lengths in men with LOH.

Methods: We reviewed the medical records of 428 men with LOH who had been treated with TU and 5 patients were diagnosed with prostate cancer during TU therapy. There were 120 patients (mean age = 65.6 ± 8.9 years) who had 5 to 8 years of continuous TU supplementation and sufficiently completed records for analysis. Genomic DNA was extracted from peripheral blood and the CAG repeat region was amplified by polymerase chain reaction. Fragment analysis, sequencing, electropherography, and chromatography were performed.

Main Outcome Measures: The main outcome measure was dynamic parameter changes during testosterone supplementation.

Results: TU did not improve all obesity parameters. A statistically significant decrease was found in waist circumference, percentage of body fat, glycated hemoglobin, cholesterol, low-density lipoprotein, and International Prostate Symptom Score ($P < .05$). TU did not produce differences in body mass index, high-density lipoprotein, triglyceride, or the Aging Male Symptoms score from baseline. However, a statistically significant increase was found in the level of testosterone, prostate-specific antigen, hematocrit, International Index of Erectile Function score, and vertebral and femoral bone mineral density ($P < .05$). No major adverse cardiovascular events or prostate cancer occurred during this study. The CAG repeat length was 14 to 28 and the median CAG length was 22. There was no association between CAG repeat length and any of the anthropometric measurements.

Conclusion: Long-term TU treatment in men with LOH for up to 8 years appears to be safe, tolerable, and effective in correcting obesity parameters.

Key Words: Androgen Receptor; Late-Onset Hypogonadism; Metabolic Syndrome; Obesity; Prostate Cancer; Testosterone

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INTRODUCTION

A previous meta-analysis of injectable testosterone undecanoate (TU) showed positive outcomes on body composition, weight, and glycol metabolic profile in observational trials, such as decreases in fat mass and glycated hemoglobin (HbA_{1c}), improvement of erectile function, and the amelioration of several other factors, including blood pressure, lipid profile, waist circumference, and body mass index (BMI), but limited evidence in randomized controlled trials.[1] TU treatment was effective and safe and no risk of prostate cancer or cardiovascular disease was

reported. Similarly, a more recent meta-analysis on the effect of testosterone replacement therapy (TRT) in randomized controlled trials documented no modification of body weight.[2] Specifically designed studies and longer follow-ups are required to confirm the results.

If the androgen receptor (AR) CAG repeat polymorphism is increased, then a decrease of sensitivity of AR occurs. The numbers of this gene range from 9 to 35 for most people. The average length of the CAG repeat polymorphism differs by ethnicity (18−20, 21−22, and 22−23 for Africans, Europeans, and Eastern Asians, respectively).[3−5]

The Massachusetts Male Aging Study found that total and free testosterone (T) levels are positively correlated with the CAG repeat number[6]; however, this has not been confirmed in other studies. The pharmacogenetic influence of the CAG repeat polymorphism of the AR gene on BMI, or age, also might play a long-term role in safety aspects. It has been demonstrated that the effects of other T preparations, such as short-acting intramuscular injected esters and transdermal and oral preparations, are modulated by this polymorphism.[7] The AR gene CAG repeat lengths in Thai men with late-onset hypogonadal (LOH) have not been studied previously.

Previously, we reported that administration of TU to men with symptoms of LOH improved body composition, lipid profiles, and psychological and sexual functions and appeared acceptably safe with a mean duration of treatment of 3.2 years.[8] Francomano et al[9] reported that 5-year treatment with TU was safe and effective in relation to metabolic syndrome (MetS) and did not negatively affect lower urinary tract symptoms (LUTS) and prostate volume. However, the longer follow-up effects of intramuscular TU therapy on metabolic parameters, urinary symptoms, bone mineral density (BMD), and sexual function are needed.

AIMS

The objectives of this study were to assess the long-term 8-year follow-up and sustained effect of injection TU therapy on metabolic parameters, urinary symptoms, BMD, and sexual function and investigate AR gene CAG repeat lengths in Thai men with LOH.

METHODS

Study Design

LOH is defined as "a clinical and biochemical syndrome associated with advancing age and characterized by typical symptoms and a deficiency in serum testosterone levels. It may significantly reduce quality of life and adversely affect the function of multiple organ systems."[10] To meet the criteria for the diagnosis of LOH, patients need to report symptoms of androgen deficiency and have a total serum T level lower than 300 ng/dL.

Serum total T and SHBG were measured with a solid-phase, competitive, two-site chemiluminescent immunometric assay using commercially available kits (IMMULITE; Siemens Healthcare Diagnostic Products Ltd, Llanberis, Gwynedd, UK). Analytical sensitivities of total T and SHBG were 15 ng/dL (0.5 nmol/L) and 0.02 nmol/L, respectively.

Diagnosis also depends on the exclusion of other diseases, such as karyotyping (Klinefelter syndrome), secondary hypogonadism, or a history of testicular inflammation (ie, orchitis). We followed the new International Society of Andrology, International Society for the Study of the Aging Male, European Association of Urology, European Academy of Andrology, and American Society of Andrology recommendations on the investigation, treatment, and monitoring of LOH in men: "3.3. Measurements of serum [luteinizing hormone] will assist in differentiating between primary and secondary hypogonadism and serum prolactin is indicated when the serum testosterone is lower than 5.2 nmol/L (150 ng/dL) or when secondary hypogonadism is suspected (level 3, grade B)."[10−12]

According to the harmonized criteria for MetS, the definition of obesity differs for different ethnic groups. For Asian men, a waist circumference of at least 90 cm is the threshold for abdominal obesity.[13]

General physical examination and measurement of anthropometric parameters (ie, height, weight, and waist circumference) were performed at baseline and at each visit, and blood samples were drawn at each or every other visit before the next injection of TU. Before patients were eligible for TU administration, we performed complete blood cell counts, liver function tests, lipid profile, levels of total T, prostate-specific antigen (PSA), digital rectal examination (DRE), transrectal ultrasonography, and BMD at baseline and biannually. Dual-energy x-ray scanners (model DPX-IQ; Lunar Radiation Corp, Madison, WI, USA) were used to measure body fat. Percentage of body fat was calculated as the ratio of fat mass to total body weight. Men with LOH received intramuscular injections of TU 1,000 mg at day 1, at week 6, and every 10 to 14 weeks thereafter.

This observational study, which did not use experimental drugs or procedures, was approved by the local ethical review board and conducted according to the principles of the Declaration of Helsinki with regard to protocol and Good Clinical Practice. Written informed consent was obtained from each patient before conducting the questionnaires and gene investigation. Patients also were advised to exercise regularly and maintain a healthy lifestyle for the duration of the study.

Exclusion Criteria

To avoid any decrease in patient numbers during the course of the long-term study, patients with a minimum of 5 years' continuous TU supplementation and a maximum duration of 8 years and sufficiently completed records to allow analysis were selected. Exclusion criteria were history of breast or prostate