Could Testosterone Replacement Therapy in Hypogonadal Men Ameliorate Anemia, a Cardiovascular Risk Factor? An Observational, 54-Week Cumulative Registry Study

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Purpose: In this study we investigated if testosterone undecanoate attenuates anemia and the risk of cardiovascular disease in patients with hypogonadism.

Materials and Methods: A registry study consisted of 58 participants with a subnormal total testosterone level (less than 2.35 ng/ml) and at least mild symptoms of testosterone deficiency. All patients received an injection of 1,000 mg testosterone undecanoate at the initial visit, followed by injection at 6, 18, 30, 42 and 54 weeks. Serum hormones, hemoglobin, hematocrit, anemia risk factors, lipid profiles, whole blood viscosity and anthropometry were measured.

Results: Total testosterone (from mean ± SD 1.87 ± 1.09 to 5.52 ± 1.92 ng/ml, $p < 0.001$) and free testosterone (from 3.04 ± 2.03 to 7.23 ± 2.90 pg/ml, $p < 0.001$) were restored by testosterone undecanoate therapy. Hemoglobin and hematocrit significantly increased after testosterone undecanoate therapy by an average of 2.46 gm/dl ($p < 0.001$) and 3.03% ($p < 0.001$), respectively. The prevalence of anemia (from 29.6% to 10.0%) significantly decreased ($p < 0.001$) and patients with anemia showed a significant increase in erythropoietin after testosterone undecanoate therapy ($p = 0.047$). A reduction in total cholesterol (from 165.89 ± 39.16 to 153.80 ± 154.27 mg/dl, $p = 0.002$), increased whole blood viscosity and increased hematocrit were observed until 54 weeks compared with baseline. However, whole blood viscosity and hematocrit stabilized after 18 weeks.

Conclusions: After 54 weeks testosterone undecanoate decreased the prevalence of anemia and components of the metabolic syndrome. A longer duration of testosterone undecanoate therapy of more than 18 weeks may be effective and safe in reducing blood viscosity and improving anemia.

Abbreviations and Acronyms

BMI = body mass index
CVD = cardiovascular disease
ESR = erythrocyte sedimentation rate
FT = free testosterone
Hb = hemoglobin
Hct = hematocrit
HDL = high-density lipoprotein
hs-CRP = high sensitivity C-reactive protein
LDL = low-density lipoprotein
TC = total cholesterol
TDS = testosterone deficiency syndrome
TIBC = total iron binding capacity
TRT = testosterone replacement therapy
TT = total testosterone
TU = testosterone undecanoate
UIBC = unsaturated iron binding capacity
WBV = whole blood viscosity

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MALE hypogonadism results from failure of the testes to produce adequate sex hormones, which may be due to distant or local hormonal deficiency.[1] Normal aging could be one of the causes of the deficiency. Collectively referred to as TDS, the associated symptoms may be erectile dysfunction, increased abdominal fat and reduced muscle.[2] Low circulating testosterone is also linked to conditions such as anemia, metabolic syndrome and CVD.[3]

From the Massachusetts Male Aging Study of older men (1987 to 2004) the average age related reduction in TT is 0.8% to 1.6% per year after age 40.[4] Anemia is a frequent finding in hypogonadal men as testosterone stimulates erythropoiesis in a dose dependent manner and more prominently in older men, despite the effect being independent of actual erythropoietin and transferrin receptor levels.[5–7] It is reasonable to hypothesize that a decrease in testosterone levels in males with TDS may lead to anemia and increase the risk of CVD.

The mechanism linking TDS with the metabolic syndrome seems to be complicated and multidirectional.[8,9] The metabolic syndrome is known to be associated with an increasing risk of CVD. Hematological parameters such as increased WBV, increased erythrocyte aggregation, reduced erythrocyte deformability and altered erythrocyte morphology have also been associated with the metabolic syndrome and CVD.[10–12]

We investigate whether a TU formulation, Nebido®, has a sustained benefit on anemia as well as metabolic and CVD parameters in men with TDS. We also measured any dynamic alterations in blood viscosity by TU and its relationship to the risk of CVD in patients with testosterone deficiency syndrome. Nebido was approved as AVEED® (3 ml TU) by the U.S. Food and Drug Administration.

MATERIALS AND METHODS

Ethics and Informed Consent

This study was conducted at Chonbuk National University Hospital. Written informed consent was obtained from all subjects before study enrollment. Study protocols and informed consent forms were approved by the institutional review board (number CUH 2015-06-133-001, Clinical Research Information Service KCT0001680).

Study Design

This study was an open label, cumulative analysis of adult males with TDS, conducted starting in February 2012. The last subject completed the study in June 2015. Parameters were measured during the initial screening visit (visit 1), followed by measurements at 6, 18, 30, 42 and 54 weeks after the initial injection (fig. 1).

Subjects

The study population was comprised of hypogonadal patients who were selected to participate in the open label, cumulative registry study. The subjects were male, age 18 to 80 years, with a BMI of 18 to 40 kg/m^2. The individuals had to have a serum TT level less than 2.35 ng/ml and at least mild TDS to be included in the study. Most hypogonadal men had not received any previous androgen treatment, and those who had needed to have discontinued testosterone treatment for at least 6 months before enrollment in the study. The patients had a rectal examination, transrectal ultrasonography and prostate specific antigen levels checked before treatment.

The enrolled group (58) received active treatment during the open phase of the study, and of these patients 29 dropped out before visit 3 due to financial status (22) or lack of symptom improvement (7). The patients received an injection of 1,000 mg TU in the ventrogluteal muscle of the hip on the initial visit, followed by injection at 6, 18, 30, 42 and 54 weeks.

Study exclusions were for tobacco smoking, prostate specific antigen greater than 2.5 ng/ml, a current or previous diagnosis of prostate cancer, International Prostate Symptom Score greater than 15, an untreated prolactinoma, Hct greater than 52% or Hb greater than 18 gm/dl, uncontrolled diabetes mellitus (hemoglobin A1c above 10%), liver and kidney disease, and known diseases of the testis or the pituitary.

General and Biochemical Analyses and Hormone Measurement

A venous blood sample was drawn for complete blood count, TC, triglyceride, HDL, LDL, fibrinogen, glucose, hs-CRP and ESR. TT evaluations were always made between 8:00 and 10:00 a.m. Hormonal tests included TT (Coat-A-Count® Testosterone, Siemens Healthcare Diagnostics Inc,

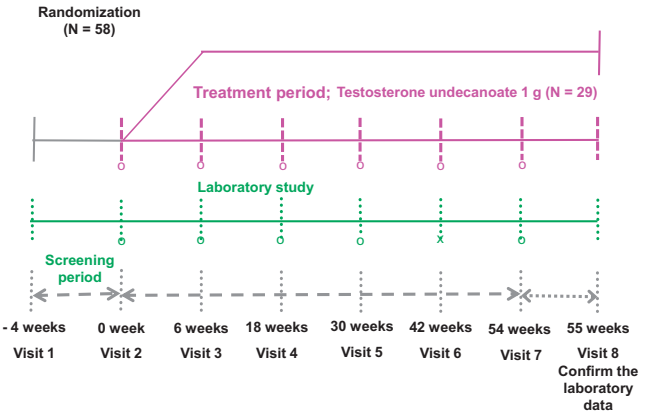

Figure 1. Schedule of testosterone undecanoate