Predicting Biochemical Response to Clomiphene Citrate in Men with Hypogonadism

Clarisse R. Mazzola, MD,* Darren J. Katz, MD,*† Nina Loghmanieh, DO,* Christian J. Nelson, PhD,* and John P. Mulhall, MD*

*Sexual Medicine Clinic, Memorial Sloan-Kettering Cancer Center, New York City, NY, USA; †Urology Department, Western Health, Footscray, Vic., Australia

DOI: 10.1111/jsm.12592

ABSTRACT

Introduction. Clomiphene citrate (CC) is as an effective treatment for men with hypogonadism (HG). Identifying the ideal candidate for this strategy has to date largely relied upon a patient's interest in preservation of testicular volume and spermatogenesis.

Aim. This analysis was undertaken to define if predictors existed of robust elevation in serum testosterone (T) levels in response to CC.

Methods. Seventy-six men with a diagnosis of HG (two separate early morning total T levels <300 ng/dL) opting for CC therapy constituted the study population. Demographic, comorbidity data, and physical and laboratory characteristics were recorded. Laboratory tests were conducted 4 weeks after commencement and every 6 months thereafter. Multivariable analysis was conducted to define if predictors of biochemical response could be identified. Parameters included in the model were patient age, mean testicular volume, varicocele presence, and baseline total T, free T, and luteinizing hormone (LH) levels.

Main Outcome Measure. Successful biochemical response to CC, defined as an increase of ≥200 ng/dL in total T level at ≥6 months after commencing CC, was the main outcome measure.

Results. Mean age was 46 ± 22 years. Mean pretreatment testicular volume was 16 ± 8 mL. Mean baseline T and LH levels were 179 ± 72 ng/dL and 7.2 ± 5.6 IU/mL, respectively. Mean total T on CC was 467 ± 190 ng/dL. Forty-seven patients (62%) met the responder definition, with a mean increase in total T levels of 302 ± 76 (204–464) ng/dL. In CC responders, the mean LH rise was 5.6 ± 3.1 IU/mL. On multivariable analysis, factors predictive of CC response included: mean testicular volume (adjusted [adj.] $r = 0.32$, $P < 0.01$), mean testicular volume ≥14 mL (hazard ratio [HR] 2.2, $P < 0.01$), LH level (adj. $r = 0.48$, $P < 0.001$), and LH level ≤6 IU/mL (HR 3.5, $P < 0.001$).

Conclusion. These data indicate that two thirds of men with HG meet a robust responder definition and that pretreatment testicular volume and LH levels (in continuous and dichotomized fashions) are predictors of response.

Mazzola CR, Katz DJ, Loghmanieh N, Nelson CJ, and Mulhall JP. Predicting biochemical response to clomiphene citrate in men with hypogonadism. J Sex Med 2014;11:2302–2307.

Key Words. Hypogonadism; Clomiphene Citrate; Testosterone; Testosterone Replacement Therapy; Infertility; Testicular Atrophy; LH; Secondary Hypogonadism

Introduction

Hypogonadism (HG) is estimated to affect approximately five million men in the United States, with a significant negative impact on the health-related quality of life in the affected men [1–3]. While it is most commonly seen in the older population, it can also occur in younger men [4]. Two main forms of HG have been identified: primary HG is the result of gonadal dysfunction

(testicular failure) whereas secondary (central) HG is caused by dysfunction of the hypothalamic–pituitary–gonadal (HPG) axis [5,6]. Chief complaints leading to diagnosis are usually sexual dysfunction and infertility issues, but the diagnosis can also be made in the workup of more aspecific conditions such as depression, osteoporosis, metabolic syndrome, and cardiovascular disease [4,7–12]. While the diagnosis only requires clinical evaluation and an early morning (prior to 10AM) testosterone (T) testing, the rate of underdiagnosis is likely high, and it is estimated that only 5–10% of HG patients are actively treated [2].

Until very recently, treatment options have mainly consisted of T replacement using a variety of modalities [13]. However, exogenous T administration leads to suppression of luteinizing hormone (LH) and follicle-stimulating hormone secretion, and this is problematic for patients wishing to remain fertile, as it can lead to impaired spermatogenesis, and with time, testicular atrophy [14–16].

Among non-T-based strategies available [16] and apart from human chorionic gonadotropin, clomiphene citrate (CC) has shown promising efficacy and may fulfill this need. As a selective estrogen receptor modulator (SERM), it acts on the HPG axis and increases gonadotrophin levels, which in turn stimulates T production [17–20]. This pharmacology makes it particularly interesting in younger patients with secondary HG who wish to remain fertile [18,19].

Aims

Several studies have evaluated the efficacy and safety of CC therapy in the HG patients' population and have demonstrated that CC can effectively increase both gonadotropins and T [18–20]. However, no research to date has attempted to define predictors of response to CC therapy.

This analysis was undertaken to evaluate biochemical response to CC and define if predictors existed of robust elevation in serum T levels in response to CC.

Methods

Study Design

This is a retrospective study of prospectively acquired data. Our database was registered with the institutional review board.

Patient Population

Between 2002 and 2006, patients referring to our sexual medicine clinic with symptoms consistent with HG, (i) erectile dysfunction; (ii) bilateral testicular atrophy; and (iii) infertility, or any combination thereof, had their serum T measured. All patients were naïve to prior hormone replacement therapy of prior anabolic steroid use. If the baseline T measurements were abnormal, the T (total and free), sex hormone-binding globulin, LH, and estradiol levels were remeasured along with a serum prolactin level and thyroid function tests when appropriate. When serum total T level was measured less than 300 ng/dL on 2 early morning (between 7 and 11AM according to the international guidelines) measurements, patients were considered to have HG.

Patients were then counseled by the treating physician regarding the risks and benefits of direct T supplementation in its various forms vs. the use of CC therapy. We specifically highlighted the concept of testicular atrophy with direct T supplementation and the absence of this concern when using CC. Patients who opted for CC with at least 6-month follow-up constituted our study population, representing a total of 76 consecutive patients. They were then commenced on CC 25 mg every other day.

In this study population, in addition to laboratory tests, patient demographics, comorbidities, varicocele status (presence, grade), and treatment data were recorded. Testicular volumes were measured by a single examiner using a Prader orchidometer and were also recorded.

Statistical Analysis

Univariate analysis was used to study categorical and numerical data. Comparisons were performed using the chi-squared test for categorical variables and the Mann–Whitney *U*-test for continuous variables. Multivariable analysis was conducted to define if predictors of such a response could be identified. The regression model included these parameters: patient age, mean testicular volume, varicocele presence, varicocele grade, presence of diabetes, and baseline total T, free T, and LH levels.

Main Outcome Measures

Laboratory tests were conducted all in the same laboratory 4 weeks after commencement, and every 6 months thereafter. Total T was measured