Predicting Biochemical Response to Clomiphene Citrate in Men with Hypogonadism

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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.

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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

Table 1 Patients' characteristics

Characteristic	
Age, mean ± SD (range), years	46 ± 22 (21–67)
Hypertension (%)	27
Hyperlipidemia (%)	33
Smoking (%)	19
Diabetes (%)	12
Varicocele grade II or III (%)	18.4
Unilateral (%)	11.8
Bilateral (%)	6.6
Testicular volume (mL)	16 ± 8

SD = standard deviation

using liquid chromatography mass spectroscopy, free T was calculated, and estradiol 2 (E2) was measured by mass spectrometry. In our study, successful biochemical response to CC was arbitrarily defined by us as an increase of ≥200 ng/dL in total T level at ≥6 months combined with a posttreatment serum level ≥400 ng/dL at ≥6 months after commencing CC. Patients failing to respond (increase of <200 ng/dL in total T level and/or serum level <400 ng/dL at >6 months after commencing CC) were first titrated to 50 mg every other day based on the treatment T level. In the absence of treatment response at the next laboratory testing (6 months after dose change), they were changed to daily CC use at 50 mg.

Results

Study Population

Patient characteristics are presented in Table 1.

The mean duration of therapy was 7.8 ± 4.2 (6–11) months.

Outcomes (Table 2)

At the end of the study, 32 patients were taking CC 25 mg every other day, 17 patients CC 50 mg every other day, and 27 patients CC 50 mg daily. There was no dropout of therapy. Mean baseline T and LH levels were 179 ± 72 (96–284) ng/dL and 5.2 ± 5.6 (1.1–12.8) IU/mL, respectively. Mean total T on CC was 467 ± 90 (402–678) ng/dL. Forty-nine patients (64%) met the responder definition, with a mean increase in total T levels for responders of 288 ± 76 (204–464) ng/dL. In CC responders, the mean LH rise was 5.6 ± 3.1 IU/mL. As CC is a SERM, our table also reports the estradiol measurements performed on our patients with a significant increase of E2 from 29 ± 31 to 42 ± 20 pg/mL ($P < 0.01$). None of the patients, however, had any symptoms associated with an increase in their serum E2 (gynecomastia, nipple tenderness) or reduction in libido. We therefore believe that the elevation noted in the study was not clinically significant. Of note, the T/E2 ratio changed throughout the study, going from 6.2 to 11.2 at the end of the study.

Multivariable Analysis (Table 3)

Factors predictive of CC response included: mean testicular volume (adjusted [adj.] $r = 0.32$, $P < 0.01$) and LH level (adj. $r = 0.48$, $P < 0.001$). Using receiver-operating characteristic curves, we determined that a mean testicular volume ≥14 mL and LH level ≤6 IU/mL were able to predict successful response to CC with hazard ratio (HR) 2.2, $P < 0.01$ and HR 3.5, $P < 0.001$, respectively.

Discussion

Although the published reports on the use of CC in HG patients to date are few, it is now well established that CC is a safe and effective treatment of HG. Besides the dose-dependent side effects that have been reported to date, such as vasomotor flushes, (10.4%), abdominal discomfort (5.5%), nausea and vomiting (2.2%), and headaches (1.3%), the occurrence of visual symptoms (flashes, central and peripheral scotomas, blurred vision, photophobia, and palinopsia) in 1.5% of cases has nevertheless been considered to date as a contraindication of treatment continuation [21]. While those symptoms are usually minimal and disappear with cessation of treatment, the cases of three patients with permanent visual sequelae have

Table 2 Hormone outcomes

	Baseline	Treatment	*P* value
Mean total T (ng/dL)	179 ± 72	467 ± 190	<0.01
Mean free T (pg/mL)	26 ± 19	76 ± 54	<0.01
Mean E2 (pg/mL)	29 ± 31	42 ± 20	<0.01
Mean LH (IU/mL)	5.2 ± 5.6	10.8 ± 3.8	<0.01

E2 = estradiol 2; LH = luteinizing hormone; T = testosterone

Table 3 Multivariable analysis of predictors of successful biochemical response to clomiphene citrate

Factors			
Continuous variables	adj. *r*		*P* value
Mean testicular volume	0.32		<0.01
LH level	0.48		<0.001
Dichotomous variables	HR	95% CI	*P* value
Testicular volume ≥14 mL	2.2	1.4–5.2	<0.01
LH level ≤6 IU/mL	3.5	1.9–7.8	<0.001

adj. *r* = adjusted ratio; CI = confidence interval; LH = luteinizing hormone; HR = hazard ratio

indeed been reported [22,23]. Of note, most of the published data regarding the side effects of CC were observed in women treated with CC.

Regarding efficacy of treatment, in a study by Shabsigh et al., performed on 36 patients, the authors showed that daily 25 mg CC was able to make mean total T levels rise from 247 to 610 ng/dL after 4–6 weeks treatment [24]. In another study by Taylor et al., the same biochemical effects were observed in 65 patients with a rise of T from 277 ng/dL to 573 ng/dL after an average treatment duration of 23 (8–40) months with 50 mg CC daily. In this study, the authors showed that these biochemical effects also translated into a significant decrease in the androgen deficiency of the aging male (ADAM) questionnaire scores from 4.9 at baseline to 2.1 at follow-up [20,25].

In 2011, Moskovic et al. validated those results, also demonstrating a significant improvement in bone densitometry in their study population of 46 HG patients, with a proportion of patients with osteoporosis decreasing from 13% at baseline to 3% at the 3-year follow-up time-point, using 25 mg or 50 mg CC every other day [19]. In this study, with a mean follow-up of more than 12 months, patients had a significant improvement in their ADAM scores, and their T levels were shown to increase from 228 ng/dL at baseline to 612 ng/dL at 1 year, 562 ng/dL at 2 years, and 582 ng/dL at 3 years ($P < 0.001$) [19]. In a more recent study by the same authors, these results were confirmed in a larger cohort of 86 patients [18]. In all the aforementioned studies, no significant adverse effects were reported [18–20,24,26].

In our current study, we found that the CC response rate was 62%. In other words, CC treatment was not beneficial in 38% of patients, which is a point that was not clearly highlighted in the aforementioned studies. One exception to that is the study by Guay et al., in which a 38.7% total response and a 36.4% partial response rates were observed [27]. However, in this study, a successful and a partial response were defined as the ability to complete intercourse in more than 75% of attempts and in 50–75% of attempts, respectively, while our definition was strictly laboratory based and thus less subjective [27]. Our results are also in keeping with the results of a prior study, in which the authors reported that 30% of patients had to be up-titrated to 50 mg CC every other day, and CC treatment was reported to have no symptomatic impact on 10% of men, suggesting significant interindividual variability in CC response [18]. A potential explanation for that could well be the genetic polymorphism of cytochrome P450 2D6 [28]. Indeed, according to a study by Mürdter et al., the formation of the active clomiphene metabolites (E)-4-hydroxyclomiphene and (E)-4-hydroxy-N-desethylclomiphene was shown to be strongly dependent on the polymorphic CYP2D6 enzyme [28]. Another factor that could explain a suboptimal response in some men could also be the currently available formulation of CC. Indeed, it contains a mixture of a trans isomer (enclomiphene) and a cis isomer (zuclomiphene), the latter having a greater estrogenic activity and a longer half-life.

There might also be some intraindividual variability in CC response. In one study, there was an excellent continued T response to CC after 12 months, with a mean rise of total T levels of 384 ng/dL, followed by a slight drop of total T levels over the next 24 months [19]. Furthermore, the ADAM score was shown to initially decrease, but increased again over the 36-month follow-up period ($P = 0.01$) [19].

Differences in susceptibility of each individual to respond to CC raise the question on how to define the ideal candidate for CC treatment. In our series, predictors of response included: mean testicular volume (as a continuous variable), especially a mean testicular volume ≥14 mL, and LH level (as a continuous variable), especially a mean LH level ≤6 IU/mL at treatment commencement.

The underlying mechanism by which a high testicular volume is associated to CC response is likely related to a threshold volume of Leydig cells capable of responding to LH stimulation. Regarding LH levels, the pretreatment levels we found in our cohort were comparable with that observed in the study by Shabsigh et al.: 2.3 ± 2.3 IU/L, Moskovic et al.: 2.0 ± 1.6 IU/L, Katz et al.: 2.6 ± 2.2 IU/L, but lower than the ones reported in the study by Taylor and Levine: 3.57 (0.02–11.6) IU/L [18–20,24]. In our study, the patients with the highest LH levels had the poorest response to CC. This is most probably due to the fact that patients with low T and elevated LH levels most probably already have maximum stimulation of their Leydig cells by LH and thus struggle to generate greatest T production. These results seem in keeping with the study by Guay et al. [27]. Indeed, in their study, two predictors of response were found: a younger age and the absence of a venous leak [27]. To our knowledge, ours is the first study to address the issue of the predictors of CC response in patients with HG. And we believe our

study is all the more important as a new formulation of CC containing only the trans isomer of CC, enclomiphene, is currently being tested and is in phase II trials with the Food and Drug Administration.

This study is somewhat limited given its small patient numbers, although on multivariable analysis, given that we have a prediction model incorporating only six factors, a population of 76 patients should be enough to generate a robust multivariable model. Another limitation is that the responder definition was chosen by us and is not a universally accepted definition. However, no other such definition exists in the literature. As our study only aimed at assessing biochemical response in patients under CC compared with patients without treatment, we also did not have a control group with patients under T replacement therapy. The strengths of our study include its being a prospective study and using a rigorous definition of HG and a biochemically objective definition for response to CC.

Conclusion

These data indicate that about two thirds of men with HG have a significant serum T response to CC. Our data support pretreatment testicular volume and LH levels (in continuous and dichotomized fashions) as predictors of response.

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