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Clomiphene citrate is safe and effective for long-term management of hypogonadism

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What's known on the subject? and What does the study add?
Clomiphene citrate (CC) has previously been documented to be efficacious in the treatment of hypogonadism. However little is known about the long term efficacy and safety of CC. Our study demonstrates that CC is efficacious after 3 years of therapy. Testosterone levels and bone mineral density measurement improved significantly and were sustained over this prolonged period. Subjective improvements were also demonstrated. No adverse events were reported.

OBJECTIVE

- To assess the efficacy and safety of long-term clomiphene citrate (CC) therapy in symptomatic patients with hypogonadism (HG).

PATIENTS AND METHODS

- Serum T, oestradiol and luteinizing hormone (LH) were measured in patients who were treated with CC for over 12 months.
- Additionally, bone densitometry (BD) results were collected for all patients. Demographic, comorbidity, treatment and Androgen Deficiency in Aging Men (ADAM) score data were also recorded.
- Comparison was made between baseline and post-treatment variables, and multivariable analysis was conducted to define predictors of successful response to CC.
- The main outcome measures were predictors of response and long-term results with long-term CC therapy in hypogonadal patients.

RESULTS

- The 46 patients (mean age 44 years) had baseline serum testosterone (T) levels of 228 ng/dL.
- Follow-up T levels were 612 ng/dL at 1 year, 562 ng/dL at 2 years, and 582 ng/dL at 3 years ($P < 0.001$).
- Mean femoral neck and lumbar spine BD scores improved significantly.
- ADAM scores (and responses) fell from a baseline of 7 to a nadir of 3 after 1 year.
- No adverse events were reported by any patients.

CONCLUSIONS

- Clomiphene citrate is an effective long-term therapy for HG in appropriate patients.
- The drug raises T levels substantially in addition to improving other manifestations of HG such as osteopenia/osteoporosis and ADAM symptoms.

KEYWORDS

hypogonadism, clomiphene, testosterone, bone mineral density

INTRODUCTION

Hypogonadism, defined as a low serum testosterone (T) accompanied by a constellation of symptoms, is of growing concern to clinicians, as the prevalence in the US has increased over time. Additionally, T levels in ageing men decline ≈ 10–15% per decade [1,2]. Two forms of hypogonadism (HG) have been identified: primary HG is the result of gonadal dysfunction, whereas secondary HG is caused by dysfunction of the central component of the hypothalamic–pituitary–gonadal (HPG) axis. Given the unique pathogenesis of primary vs secondary HG, treatment of the former can be achieved with direct replacement of T, while the latter pathology is amenable to therapy through stimulation of HPG-axis gonadotrophin release. It might be important to differentiate between the aetiology of HG in some patients, considering the side-effects of direct T replacement, specifically testicular atrophy and fertility, which could be avoided by utilizing non-T-based strategies, such as clomiphene citrate or hCG [3].

Clomiphene citrate (CC), a selective oestrogen receptor modulator (SERM), has been of increasing interest to practitioners managing secondary HG [4–6]. Several studies have evaluated the efficacy and safety of CC therapy in this population where short-term therapy has yielded improvements in T levels and HG

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TABLE 1 Baseline and follow-up hormone, symptom and BMI data for patients (data are means ± SD)

	Baseline	Year 1	Year 2	Year 3	*P* value
Total T, ng/dL	228 ± 48	612 ± 212	562 ± 201	582 ± 227	<0.001
LH, IU/mL	2.0 ± 1.6	8.6 ± 3.2	7.2 ± 4.0	8.2 ± 1.9	<0.001
Oestradiol, pg/mL	37 ± 16	48 + 22	42 ± 13	50 ± 30	0.02
ADAM (+ responses)	7 ± 2	3 ± 2	5 ± 2.5	5 ± 3	0.01
Mean BMI, kg/m^2	32 ± 8	31 ± 9	29 ± 11	28 ± 4	<0.05

symptomatology. The studies have also demonstrated that CC can effectively increase both gonadotrophins and T.

Some have expressed concern regarding the effect of chronic CC treatment on bone density given its anti-oestrogenic effects. Given the paucity of long-term experience with CC, we reviewed the outcomes of long-term CC therapy.

PATIENTS AND METHODS

The study population comprised patients with HG seen between 2002 and 2006 who were treated with CC for ≥12 months and underwent annual bone densitometry. HG was defined as a serum total T level <300 ng/dL on two consecutive early morning (before 10.00 am) total T measurements. Serum androgens and gonadotrophins (luteinizing hormone [LH], follicle-stimulating hormone [FSH]) were measured in patients if they had symptoms consistent with HG, erectile dysfunction, testicular atrophy, a clinically significant (grade II or III) varicocele or infertility. If the baseline T measurements were abnormal, the T (total and free), sex hormone-binding globulin and oestradiol concentrations were remeasured along with a serum prolactin level and thyroid function tests. When low serum T was confirmed on the second measurement, a bone densitometry was performed on all patients to define their bone mineral density. Patient demographics, comorbidities, testicular volumes (based on orchidometer assessment), varicocele status (presence, grade) and treatment data were also recorded.

All patients had a discussion with the treating physician regarding risks and benefits of both exogenous testosterone supplementation, including the concerns about azoospermia induction, and testicular atrophy. They were also informed about the role of CC and hCG in this clinical scenario and the avoidance of testicular atrophy concerns with these options. Patients with serum LH concentrations in the low or normal range were informed of their candidacy for CC (≤6 IU/mL). Patients opting for CC with at least 12 months of follow-up constituted the study population. Patients were commenced on CC 25 mg every other day and were titrated to 50 mg every other day based on the treatment serum T level. The target total T level was arbitrarily set at 550 ± 50 ng/dL.

At baseline and during treatment, T (free and total), sex hormone-binding globulin, oestradiol, LH and FSH were measured. The initial post-treatment hormone estimation was performed 1 month after commencing CC. Once the target T level was achieved, T/gonadotrophin levels were measured twice per year. In cases where the target T level was not achieved, further discussions were held with the patient regarding the use of intra-muscular [i.m.] hCG. The Androgen Deficiency in Aging Men (ADAM) questionnaire was administered pre-treatment and during follow-up [7]. This is a 10-question validated questionnaire focusing on key clinical features of HG. Our analysis focused on laboratory and questionnaire values attained at baseline and at the last follow-up date while still on treatment.

For statistical analysis, our hypothesis was that CC therapy would result in an increase in serum androgens and gonadotrophins and that such improvements would be sustained over time; that such hormone level improvement would be represented in improvements in the ADAM questionnaire; and that bone density would not worsen over time. The statistical analyses used to assess response to treatment were as follows: chi-squared analysis for comparison of categorical variables (ADAM questionnaire questions) at baseline and after treatment; and a repeated measures *t*-test (SPSS 16.0, Chicago, IL, USA) for comparison of serial serum hormone variables and bone density scores.

RESULTS

A total of 46 patients had ≥12 months of CC treatment, 37 patients had >2 years' treatment, and 29 patients had >3 years' treatment. Mean ± SD age was 44 ± 18 years. At the time of CC commencement, the comorbidity profile was as follows: hypertension, 35%; dyslipidaemia, 30%; diabetes, 11%; cigarette smoking history (>5 pack-years), 17%; and cardiovascular disease (coronary artery disease, coronary artery bypass surgery, coronary artery angioplasty ± stenting, cerebrovascular disease, peripheral vascular disease), 13%.

At 36 months, 75% remained on CC 25 mg every other day. There was noted an excellent continued T response to CC after 12 months, with a mean rise in total T levels of 384 ng/dL (see Table 1). Total T levels dropped slightly over the next 24 months, however mean levels remained in the therapeutic target range (500–600 ng/dL) (Fig. 1). No significant increase was seen over each passing annual time-point in the proportion of patients having total T levels falling outside of the normal (35%, 32% and 31%, respectively) or the therapeutic target range (43%, 48% and 45%, respectively). LH responded appropriately with sustained elevations, with mean increases of between 5 and 6 IU/mL. A steady increase in oestradiol was seen over the study period ($P = 0.02$). However, no patient developed gynaecomastia or nipple tenderness. No patient had a testosterone/epitestosterone ratio <10 while on CC. Despite persistently raised T levels, the ADAM score, which initially decreased, increased again over the 36-month follow-up period ($P = 0.01$) (Table 1 and Fig. 1).

Figure 2 shows the outcomes of bone densitometry over the study period. Mean ± SD T scores for femoral neck/lumbar spine at baseline were −2.1 ± 1.7/−3.2 ± 2.2. These values improved significantly ($P < 0.01$ for both sites) over time, with scores at 1, 2 and 3 years being −1.2 ± 1.2/−1.6 ± 1.8, 1.3 ± 1.6/−1.6 ± 1.2 and −0.9 ± 1.2/−1.1 ± 1.0, respectively. In all, 28% of patients had

normal bone densitometry at baseline; this rose to 50%, 48% and 55% at years 1, 2 and 3, respectively. The proportion of patients with osteoporosis was 13% at baseline and 6%, 6% and 3%, respectively, at the follow-up time points.

DISCUSSION

The present study examined the impact of long-term CC therapy on hypogonadal patients with baseline LH ≤6.0 IU/mL. CC was successful in raising T levels from a baseline mean of 228 to 612 ng/dL after 1 year of therapy. This level was sustained throughout the subsequent 2 years of follow-up available. Patients also demonstrated response to therapy through improved ADAM scores and bone mineral density as assessed by annual bone densitometry scans. Additionally, BMI declined successively over the 3-year treatment period from a baseline value of 32 kg/m^2 to a final follow-up of 28 kg/m^2. Patients were free of side-effects, suggesting that CC is effective in the long-term management of HG.

While genetic forms of HG (e.g. Klinefelter's syndrome, Kallman's syndrome) are important considerations for the clinicians, most T deficiency is attributable to the natural decline in androgen in ageing men. Interestingly, primary and secondary HPG axis dysfunctions have both been identified in the pathogenesis of age-related T declines [8,9]. Clinically, the symptomatology is generally regarded to include decline in libido, erectile dysfunction and sarcopenia [10–16]. Additionally, patients often present with mood symptoms suggestive of depression, dysthymia and irritability [17]. Critically important are the risks of cardiometabolic comorbidities associated with HG, including the development of cardiovascular disease, diabetes mellitus and osteoporosis [15,16,18–20]. Treatment with T replacement might reverse these symptoms, though the extent of efficacy remains controversial [21,22].

Clomiphene citrate, a SERM, acts as a weak antagonist of oestrogen at the level of the hypothalamus, enabling inhibition of central oestrogen feedback [23]. This oestrogen blockade results in increased GnRH production. GnRH acts on the pituitary gland to increase LH and FSH, which exert their effects on the testicle by increasing Leydig cell T synthesis and Sertoli cell spermatogenesis, respectively.

Centrally acting agonists aimed at up-regulating gonadotrophin and T levels are especially valuable when the side-effects of direct T replacement are to be avoided. Patients receiving direct T replacement therapy are predisposed to testicular atrophy and azoospermia, consequences that are particularly detrimental to patients desiring fertility [24]. Direct T administration inhibits central gonadotrophin release by negatively feeding back on the HPG axis. This reduces secretion of LH and FSH. Therefore, CC has been utilized in patients with central HPG-axis dysfunction. Additionally, hCG has been successfully used to raise T levels, although it is more costly than CC and less widely adopted [25].

Given that T replacement can be achieved though a variety of routes of administration and mechanisms, it is important to consider the strengths and weaknesses of each therapy when initiating therapy [3]. In general, experience with CC has been positive, albeit in the setting of short-duration therapy. Guay *et al.* [26] presented their experience with patients managed on CC for 8 weeks. The authors noted statistically significant increases in LH, FSH and T levels, although patients did not report subjective improvements in sexual function. Importantly, at the time of the present study, validated screening and diagnostic questionnaires for androgen deficiency and sexual dysfunction were not available. Nevertheless, this must be interpreted in the context of the very short duration of therapy utilized in the present study.

Shabsigh *et al.* [4] examined a cohort of 36 patients treated with 4–6 weeks of CC therapy. In that small study, T levels rose from 248 ng/dL to 610 ng/dL. The authors emphasize that the testosterone:oestrogen ratio improved by about 60% concurrent with the rise in total T. This implies that there is a disproportionately favourable androgen response with CC. Side-effects such as hot flashes, headaches, visual disturbances and cardiovascular disorders were denied by all patients. However, the present study did not examine the impact of CC on the symptoms of androgen deficiency. Additionally, objective measures of

FIG. 1. Breakdown of bone densitometry diagnoses at baseline and over the course of CC therapy (BD, bone density).

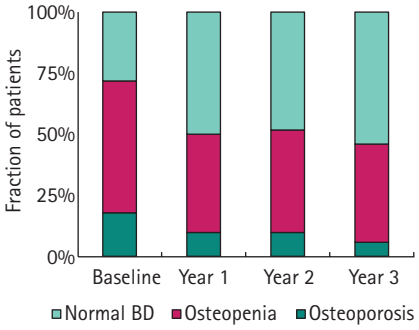
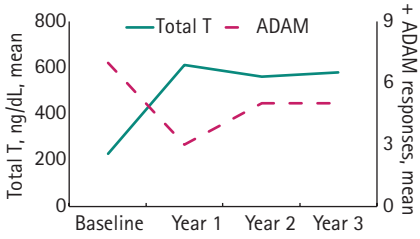


FIG. 2. Mean baseline and follow-up total T values as well as results of ADAM questionnaires quantifying the fraction of patients not reporting 'yes' for symptoms (defined as '+ response').



treatment outcomes (e.g. bone density) were not included.

A long-term comparative efficacy study between transdermal T replacement and CC was reported by Taylor & Levine [27]. That study compared 65 patients taking CC for 23 months with 39 patients treated with transdermal T for 46 months. Baseline T levels were significantly different between the two study cohorts (277 ng/dL for the CC group and 221 ng/dL for the transdermal T group), although it is unclear what impact this might have on the interpretation of the results. After therapy, T levels were observed to increase 107% and 150% in the CC and transdermal T groups, respectively. As in the present study, the ADAM questionnaire was used to follow quality-of-life outcomes, with CC patients experiencing score improvements from 4.9 to 2.1 positive responses ($P < 0.01$), and specific score improvements in the sexual function domains were also noted. One interesting observation is the less substantial baseline symptomatology in their CC group (≈ five

positive responses) than in the patients in the present study (≈ seven positive responses). No baseline ADAM data were presented for the transdermal T group. These data nevertheless suggest that CC is effective in the management of HG.

While the aforementioned data support the use of CC therapy in appropriate patients, there have been concerns raised about the efficacy of CC in older patients. Tenover *et al.* [28] compared 1 week of CC therapy in younger (22–35 years) and older (65–84 years), measuring pre- and post-treatment T and LH pulsatility. Interestingly, the authors reported a substantially weaker response to CC in the older cohort of patients (32% increase in total T vs 100% increase in the younger cohort). It is important to note that the present study characterized 'elderly' as age ≥65 years and included only 29 and 26 patients, respectively. In a follow-up study, Tenover *et al.* [29] confirmed that these findings apply in the setting of therapy of 8 weeks' duration. The results of this latter study were derived from only 10 patients evenly distributed into the age cohorts, representing a very small sample for study and, furthermore, one that was not controlled for baseline LH level. These data suggest that close follow-up of elderly patients on CC is required to ensure efficacy.

Clomiphene citrate has largely been show to be efficacious in the management of bone density in animal models [30,31]. By achieving disinhibition of central oestrogen feedback, it has even been suggested that CC could be clinically equivalent to oestrogen in the maintenance of bone density [30]. The adverse impact of diminished bone density has been clearly established; patients with osteopenia and osteoporosis are more likely to experience bone fractures and substantial quality of life impairments [32,33]. Therefore, CC might be a viable and safe option for treating hormone-dependent osteoporosis in both men and women. This observation cannot be extrapolated to the entire SERM class, which includes common chemotherapeutic drugs such as tamoxifen and raloxifene [34]. While the latter has been shown to appreciably reduce the risk of fracture in women in complement to improved bone density, the former compound has even shown increases in fracture risk for patients on long-term therapy [35]. However, these observations have not been consistent and it appears that tamoxifen is the only SERM with questionable effects on bone density [34,36]. It is possible that, while SERMS are largely anti-oestrogens in terms of their central efficacy, they are weak oestrogen agonists and therefore improve bone density directly (weak agonist activity) and indirectly (central disinhibition increasing gonadotrophin release).

The present study validates the efficacy and safety of CC when used for central stimulation of T production in hypogonadal patients. There are marked and sustained improvements in T levels, bone density outcomes and symptoms as assessed by the ADAM questionnaire. The long-term results strongly support utilization of CC for chronic therapy in appropriate hypogonadal patients (defined herein as those with LH ≤6.0 IU/mL). However, the present study has some important limitations that must be considered. As a case series, there is no comparative cohort to assess the relative efficacy of CC therapy. Additionally, some patients were lost to follow-up, diminishing the sample size over the study period and potentially confounding the results of the final follow-up period.

In conclusion, the present study has the longest follow-up of patients on CC therapy for HG. Sustained increases in T and improvements in symptoms of T deficiency and bone density were observed in this cohort. No side-effects were reported by patients in the cohort described herein. Therefore, we conclude that, in the appropriate patient, CC is an effective means of restoring androgen levels and is safe for long-term use up to 3 years.

CONFLICT OF INTEREST

None declared.

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Abbreviations: **BD**, bone densitometry; **CC**, clomiphene citrate; **FSH**, follicle-stimulating hormone; **HG**, hypogonadism; **HPG**, hypothalamic–pituitary–gonadal; **LH**, luteinizing hormone; **SERM**, selective oestrogen receptor modulator; **T**, testosterone.