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Outcomes of clomiphene citrate treatment in young hypogonadal men

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Accepted for publication 17 August 2011

Study Type – Therapy (case series)
Level of Evidence 4

What's known on the subject? and What does the study add?
Hypogonadism is a prevalent problem, increasing in frequency as men age. It is most commonly treated by testosterone supplementation therapy but in younger patients this can lead to testicular atrophy with subsequent exogenous testosterone dependency and may impair spermatogenesis. Clomiphene citrate (CC) may be used as an alternative treatment in these patients with hypogonadism when maintenance of fertility is desired.

This study shows that CC is a safe and efficacious drug to use as an alternative to exogenous testosterone. Not only have we validated previous findings of other papers but have proven our findings over a much longer period (mean duration of treatment 19 months). This prospective study is the largest to date assessing both the objective hormone response to CC therapy as well as the subjective response based on a validated questionnaire.

OBJECTIVE

- To prospectively assess the andrological outcomes of long-term clomiphene citrate (CC) treatment in hypogonadal men.

PATIENTS AND METHODS

- We prospectively evaluated 86 men with hypogonadism (HG) as confirmed by two consecutive early morning testosterone measurements <300 ng/dL.
- The cohort included all men with HG presenting to our clinic between 2002 and 2006 who, after an informed discussion, elected to have CC therapy. CC was commenced at 25 mg every other day and titrated to 50 mg every other day. The target testosterone level was 550 ± 50 ng/dL.
- Testosterone (free and total), sex hormone binding globulin, oestradiol, luteinizing hormone and follicle stimulating hormone were measured at baseline and during treatment on all patients. Once the desired testosterone level was achieved, testosterone/gonadotropin levels were measured twice per year.
- To assess subjective response to treatment, the androgen deficiency in aging males (ADAM) questionnaire was administered before treatment and during follow-up.

RESULTS

- Patients' mean (standard deviation [sd]; range) age was 29 (3; 22–37) years. Infertility was the most common reason (64%) for seeking treatment. The mean (sd) duration of CC treatment was 19 (14) months.
- At the last evaluation, 70% of men were using 25 mg CC every other day, and the remainder were using 50 mg every other day.
- All mean testosterone and gonadotropin measurements significantly increased during treatment.
- Subjectively, there was an improvement in all questions (except loss of height) on the ADAM questionnaire. More than half the patients had an improvement in at least three symptoms.
- There were no major side effects recorded and the presence of a varicocele did not have an impact on the response to CC.

CONCLUSION

- Long-term follow-up of CC treatment for HG shows that it appears to be an effective and safe alternative to testosterone supplementation in men wishing to preserve their fertility.

KEYWORDS

hypogonadism, infertility, clomiphene

INTRODUCTION

Hypogonadism (HG) is a common, yet probably under-diagnosed medical condition affecting ≈5 million men in the USA [1,2]. It is characterized by low serum testosterone levels and a non-specific constellation of symptoms. Testosterone deficiency may be attributable to a number of underlying aetiologies along the hypothalamic-pituitary-gonadal (HPG) axis. The symptoms affect multiple body systems and include low libido, decreased energy, increased fatigability, decreased strength and endurance, mood changes and bone density loss. Recent evidence suggests that HG is associated with the development of diabetes and an increased risk of cardiovascular events [3]. Not surprisingly, HG has a significant negative impact on the health-related quality of life in affected men [4].

Although HG is most commonly seen in the older population, it can also occur in younger men where it may also be associated with sexual dysfunction or infertility [5].

Despite the large number of men affected by HG, it is estimated that only 5–10% are actively treated [1,2]. HG is most commonly treated by testosterone replacement; however, exogenous testosterone affects the natural feedback mechanisms in the HPG axis, with suppression of luteinizing hormone (LH) and FSH secretion. This, in turn, can result in impaired spermatogenesis and with time, testicular atrophy [6]. For this reason, testosterone replacement is best avoided in men who wish to remain fertile. Clomiphene citrate (CC) has been used as an alternative medication for these patients. This selective oestrogen receptor modulator increases gonadotropin levels and ultimately stimulates testosterone and sperm production [7,8]; however, few studies have assessed the efficacy of CC in a prospective fashion.

PATIENTS AND METHODS

PATIENT POPULATION

We conducted a prospective evaluation of men with HG and constructed a departmental database, which was registered with the institutional ethics committee. Patients seen between 2002 and 2006 were included in the database. HG was defined as a serum testosterone <300 ng/dL on two consecutive early-morning (before 10 am) total testosterone measurements. Serum androgens and gonadotropins (LH, FSH) were measured in men presenting to our andrology clinic if they had any of the following: (i) symptoms consistent with HG, (ii) erectile dysfunction (ED), (iii) testicular atrophy, (iv) a clinically significant (grade II or III) varicocele or (v) infertility. If the baseline testosterone measurements were abnormal, the testosterone (total and free), sex hormone binding globulin (SHBG) and oestradiol levels were re-measured along with a serum prolactin level and thyroid function tests. When low serum testosterone was confirmed on the second measurement, a bone densitometry was performed to define the patient's bone mineral density. Patient demographics, comorbidities, testicular volumes (based on orchidometer assessment), varicocele status (presence, grade) and treatment data were also recorded.

TREATMENT

All patients had an extensive discussion with the treating physician regarding risks and benefits of 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 fertility concerns with these options. Patients with serum LH levels in the low or normal range (≤6 IU/mL) were informed of their candidacy for CC. Those patients who opted for CC and who had at least 6 months' follow-up constituted the study population. Patients with <6 months' follow-up were excluded, as were men with a varicocele who opted for surgical management. Treatment commenced with CC 25 mg every other day, titrating to 50 mg every other day based on the treatment serum testosterone level. The target total testosterone level was set at 550 ± 50 ng/dL.

MAIN OUTCOME MEASURES

We used both objective and subjective outcome measures. At baseline and during treatment, testosterone (free and total), SHBG, oestradiol, LH and FSH were measured. The initial post-treatment hormone estimation was conducted 1 month after commencing CC. Once a patient achieved the target testosterone level, androgen/gonadotropin levels were measured twice per year. In cases where the target testosterone level was not achieved, further discussions were held with the patient regarding the issue of i.m. hCG. The androgen deficiency in aging males (ADAM) questionnaire was administered before treatment and during follow-up [9]. This is a 10-question validated questionnaire focusing on key clinical features of HG (Appendix 1). Our analysis focused on laboratory and questionnaire values obtained at baseline and at the last follow-up date while still on CC treatment.

STATISTICAL ANALYSIS

Our hypothesis was that CC therapy would result in an increase in serum androgens and gonadotropins and that such improvements would be seen in the ADAM questionnaire. To assess response to treatment, we used: (i) chi-squared analysis to compare ADAM questionnaire results at baseline and after treatment and (ii) a repeated measures *t*-test to compare serum hormone parameters (SPSS version 16.0, Chicago, IL, USA).

RESULTS

PATIENT POPULATION

The initial population of HG patients electing to have CC treatment comprised 102 patients, but only 86 patients had ≥6-month follow-up and were analysed. Their mean (SD; range) age was 29 (3; 22–37) years. The patient population was generally very healthy, with 20% of men having one comorbidity and 4% two comorbidities. The most common comorbidity was dyslipidaemia (11%), while four (5%) men had type I diabetes. All patients had at least one symptom consistent with hypogonadism. No patient had been exposed to chemotherapy or pelvic/testicular radiation. Infertility was the presenting complaint in 49 (57%) patients, ED in 20% and low libido in 13%, while 3% presented with other symptoms. Of the 49 patients with infertility, 27 (55%) patients had at least one varicocele (12 unilateral grade II, five bilateral grade II and 10 unilateral grade III). None of these 27 patients opted for surgical intervention of their varicocele. The mean (SD; median) testicular volumes were: right 16 (6; 14) mL, left 15.5 (5.5; 15) mL, with 62% having at least one testis with a volume <16 mL. Two patients had hyperprolactinaemia; a pituitary MRI was negative in both. Of the 16 patients not analysed, nine had not yet reached the 6-month timepoint when the study ended and the other seven patients discontinued CC therapy owing to dissatisfaction with therapy, despite good LH and testosterone level responses. Three of these discontinuing patients pursued transdermal testosterone replacement therapy.

HORMONAL DATA

The laboratory values at baseline and at the last follow-up while on treatment are shown in Table 1. Nineteen percent (16/86) of patients had serum LH levels <1 IU/mL at

	Baseline, mean (SD)	After treatment, mean (SD)	*P*
Total testosterone, ng/dL	192 (87)	485 (165)	<0.01
Free testosterone, pg/mL	22 (16)	95 (35)	<0.01
SHBG, nM/L	30 (12)	32 (15)	0.72
Oestradiol, pg/mL	26 (22)	39 (18)	<0.05
LH, IU/mL	2.6 (2.2)	6.8 (2.8)	<0.01
FSH, IU/mL	1.9 (1.7)	7.6 (1.9)	<0.01

TABLE 1
Effects of CC on serum hormone profiles

P < 0.05 was considered to indicate statistical significance.

	Baseline, %	After treatment, %	*P*
Decreased libido	72	32	<0.01
Lack of energy	65	40	<0.01
Decreased strength/endurance	28	21	0.18
Lost height	4	5	0.45
Decreased life enjoyment	85	40	<0.001
Sad/grumpy	60	30	<0.01
Erections weaker	12	8	0.29
Decreased sports performance	55	25	<0.001
Sleep after dinner	34	28	0.17
Decreased work performance	45	38	0.28

TABLE 2
Alterations in individual symptoms with CC treatment based on the ADAM questionnaire

P < 0.05 was considered to indicate statistical significance.

Improvement in at least:	%
One symptom	90
Two symptoms	75
Three symptoms	60
Four symptoms	30
Five symptoms	10

TABLE 3 Symptom improvement based on the ADAM questionnaire

baseline. The mean (SD) duration of CC treatment at last follow-up was 19 (14) months. At this point, 70% of patients were using 25 mg CC and 30% were using 50 mg CC (both every other day). All mean testosterone and gonadotropin measurements significantly increased during treatment, while SHBG levels increased but not significantly. Bone densitometry analysis showed seven patients (8%) with osteopenia (three lumbar spine, two femoral neck and two both femoral neck and spine), all of whom had baseline testosterone values of <200 ng/mL.

ADAM QUESTIONNAIRE AND SAFETY OUTCOMES

Table 2 shows the results of the ADAM questionnaire. Overall, for all questions except loss of height, there was an improvement in the symptoms of HG. At baseline, the median number of 'yes' responses was 5 (interquartile range 2–7) and this dropped to 2 (interquartile range 1–4) after treatment. There was a significant improvement in five of the 10 variables (before vs after treatment): decreased libido (72% vs 32%), lack of energy (65% vs 40%), decreased life enjoyment (85% vs 40%), sad/grumpy (60% vs 30%), and decreased sports performance (55% vs 25%). Table 3 shows the proportion of patients with varying degrees of symptom improvement. More than half the patients had a subjective improvement in at least three symptoms but 10% experienced no improvement. There was no difference in response to CC in patients with or without a varicocele ($P = 0.46$). There were no major side effects recorded from CC during the course of follow-up and no patient ceased CC treatment because of adverse events.

DISCUSSION

Hypogonadism is an under-diagnosed and under-treated medical condition. It is estimated to affect up to 5 million men in the USA, yet >90% remain untreated [1,2]. Probably because of the aging US population, HG incidence is increasing; it is predicted that >6.5 million men in the USA alone will have symptomatic androgen deficiency by 2025 [2]. With aging, there is a gradual decline in serum total testosterone of 1–2% per year [5,10]. The Baltimore Longitudinal Study on Aging illustrates this, with 12% of men in their sixth decade, 19% of men in their seventh decade and 29% of men in their eighth decade having low total testosterone levels [5]. However, HG is not just a condition occurring in older patients: younger patients may also be affected but information on the prevalence of HG in younger men is scarce in comparison. In the present series of men with HG who chose to have CC treatment, the mean age was 29 years. In the Boston Area Community Health Survey, which included subjects as young as 30, there was an increase of 36% in the odds of androgen deficiency per 10-year increase in age [11].

Hypogonadism is an important condition to diagnose. Its symptoms permeate through many of the health-related quality-of-life domains [12]. In men, this includes the potential impact on physical, cognitive, emotional and sexual functioning. In addition to the well documented association with osteoporosis, metabolic syndrome and cardiovascular disease, HG has been linked to increased mortality [13–16]. Depression is another association with HG [17] and, in the present study, most patients at presentation complained of a lack of energy, feeling sad/grumpy and suffering from decreased life enjoyment. Low libido was recorded in 72% of our patients. Considering the multitude of conditions associated with HG, the potential burden on the health system is enormous.

The most commonly employed treatment for HG is exogenous testosterone administration with a target level of 400–700 ng/dL [18]. Our target of 550 ± 50 ng/dL is the midpoint between these levels. There are several administration methods and, although efficacious, each has its drawbacks. Oral therapy, one of the earliest forms of exogenous testosterone, has the disadvantages of poor bioavailability, hepatotoxicity and gastrointestinal side

effects, and while used in some countries, it is not approved by the US Food and Drug Administration (FDA) [19]. The currently available i.m. injections generally lead to large fluctuations in testosterone levels and have the potential for adverse haematological effects [20,21]. S.c. pellets have been available since the 1940s, but because a procedure is required for insertion and up to 12% of patients extrude the pellets in older series, they have not been widely used to date [22,23]. A new formulation, however, is now available in the USA (Testopel®, Slate Pharmaceuticals, Durham, NC, USA) that appears to be easier to use and extrudes less frequently. Furthermore, a long-acting i.m. injection (Nebido®, Bayer Schering Pharma, Berlin, Germany) is available in Europe and is under consideration by the FDA. Topical testosterone, historically applied by patches and more recently through gel formulations, is currently the most favoured form of administration. It allows for a more uniform absorption of the drug and is easy to administer [24].

Product labelling for exogenous testosterone states that certain patient populations have contraindications to testosterone supplementation, such as patients with prostate cancer, erythrocytosis and untreated obstructive sleep apnoea, although some of these concepts are currently being challenged [25,26]. Side effects can include acne and gynaecomastia [18]. Common to all forms of testosterone supplementation are the potential risks of testicular atrophy and infertility [6]. Testosterone has a negative feedback effect on gonadotropin secretion, which is essential to spermatogenesis. This can result in testicular atrophy and azoospermia [27]. Although this state of sub/infertility is usually reversible, these side effects are particularly worrisome for younger patients and for those older men who remain interested in fertility [27,28]; therefore, alternate means of treatment should be considered and CC represents one such strategy.

Clomiphene citrate is a weak oestrogen receptor antagonist which competes with oestradiol at the hypothalamic level [29]. Oestradiol forms part of a negative feedback mechanism which inhibits the production and release of GnRH. Thus, by competing with oestradiol, administration of CC results in an increase in GnRH which acts on the pituitary, leading to increased release of LH and FSH. LH, in turn, binds to Leydig cells and stimulates testosterone production, while FSH is critical for spermatogenesis. Thus, CC has the potential to restore the HPG axis, whereas exogenous testosterone therapy results in feedback inhibition of LH that can further exacerbate the HPG disturbance.

Despite the potential benefits of CC in treating hypogonadal men, there are only a few studies that have investigated its efficacy and safety in this setting. In an early study by Tenover *et al.* [8] five healthy young men (<34 years old) and five healthy older men (>65 years old), were given CC (100 mg daily) for 8 weeks. Testosterone increased significantly in both groups, with a greater response in the younger group. In a small double-blind, placebo-controlled crossover study of 17 men with ED and low testosterone levels, Guay *et al.* [7] showed that CC can significantly elevate LH, FSH, and testosterone (total and free) levels; however, only in younger healthier men was there an improvement in sexual function parameters. In a more recent study by the same author, a much larger cohort of 178 patients with HG and ED received CC for 4 months [30]. Again hormone levels significantly increased in all groups when categorized by erectile function response. However, multivariable analysis showed that ED response decreased with age, comorbidities and multiple medication use. Shabsigh *et al.* [31] also showed the efficacy of CC in 36 hypogonadal men. They showed that low dose CC (25 mg daily for 4–6 weeks) can significantly improve testosterone levels and significantly increase the testosterone : oestradiol ratio (8.7:14.2, $P < 0.001$). No major side effects associated with CC therapy were reported in any of these studies.

Our results validate these earlier studies regarding the efficacy of CC, but our mean duration of treatment was 19 months and therefore our study shows the efficacy of CC over a much longer period. We had a significant improvement in all clinically relevant hormone parameters. Very similar to the Shabsigh study, the mean testosterone : oestradiol ratio increased from 7.4 at baseline to 12.4 at last follow-up although no patient developed clinical gynaecomastia. From a subjective viewpoint, overall there was an improvement in all but one question on the ADAM questionnaire, though only five questions had significant differences between baseline and treatment values (Table 2). Four of these five symptoms, improvement in libido, life enjoyment, energy and mood level, have the potential to exert a meaningful impact on a man's quality of life. We chose the ADAM questionnaire as our screening tool of choice as it is relatively simple to administer, has a high sensitivity (important in a screening instrument) and has been validated in several studies [9,32]. A recent comparative study with the two other well known screening questionnaires (Aging Male Survey and Massachusetts Male Aging Study) found that the ADAM questionnaire had the highest sensitivity (97%) but the lowest specificity (30%) for diagnosing HG [32]. The majority of our patients (60%) on CC therapy had an improvement in more than three items of the ADAM questionnaire; however, administration of CC had no symptomatic impact on 10% of men, indicating that CC may not benefit all men with HG. Consistent with earlier studies, no major side effects of CC therapy were observed in our patients.

One of the strengths of this prospective study is that it is the largest to date assessing both the objective hormone response to CC therapy as well as the subjective response based on a validated questionnaire. Furthermore, it also has longer follow-up than any previous study. This is important, as it not only shows sustained efficacy but also that side effects are not associated with prolonged therapy. The weaknesses of this study include the limitations of the ADAM questionnaire; perhaps use of another, more extensive questionnaire such as the Aging Male Survey would have been more appropriate. Another limitation is the absence of a formal sexual function questionnaire such as the International Index Of Erectile Function or other quality-of-life inventories. In addition, we do not present any fertility outcomes (semen analysis changes on CC). While the present study includes a reasonable number of patients, the numbers are too small to define predictors of success with CC therapy and to determine the true impact of varicocele status on outcomes. Finally, this is of course not a randomized, placebo-controlled study, which would be

the ideal means of defining outcomes with CC in this population.

In conclusion, CC is an effective and safe alternative to testosterone supplementation therapy in hypogonadal men. The present study showed that there were significant improvements in testosterone levels with long-term CC therapy. Nearly all patients had improvement in at least one hypogonadal symptom on the ADAM questionnaire, with more than half improving in three symptoms. CC therapy has a role to play in the testosterone-deficient man and should be incorporated into the clinician-patient discussion.

ACKNOWLEDGEMENTS

Supported by The Sidney Kimmel Center for Prostate and Urologic Cancers.

CONFLICT OF INTEREST

None declared.

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Abbreviations: **CC**, clomiphene citrate; **HG**, hypogonadism; **LH**, luteinizing hormone; **ADAM**, androgen deficiency in aging males; **HPG**, hypothalamic-pituitary-gonadal; **ED**, erectile dysfunction; **SHBG**, sex hormone binding globulin; **FDA**, US Food and Drug Administration.

APPENDIX 1: ADAM QUESTIONNAIRE:

1. Do you have a decrease in libido (sex drive)?
2. Do you have a lack of energy?
3. Do you have a decrease in strength and/or endurance?
4. Have you lost height?
5. Have you noticed a decreased "enjoyment of life"?
6. Are you sad and/or grumpy?
7. Are your erections less strong?
8. Have you noted a recent deterioration in your ability to play sports?
9. Are you falling asleep after dinner?
10. Has there been a recent deterioration in your work performance?

This questionnaire is suggestive of the presence of HG when the patient answers 'yes' to items 1 or 7 or when 3 or more questions are answered affirmatively.