


Clomiphene citrate and human chorionic gonadotropin are both effective in restoring testosterone in hypogonadism: a short-course randomized study

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Objectives

To compare serum testosterone response and symptom improvement in men with hypogonadism in response to treatment with clomiphene citrate (CC), human chorionic gonadotropin (hCG), or a combination of both therapies.

Patients and Methods

A total of 282 men with hypogonadism, wishing to preserve their fertility, were randomized to one of three treatment arms: CC 50 mg ($n = 95$); 5000 IU hCG injections twice weekly ($n = 94$); or a combination of both therapies (CC + hCG; $n = 94$). All participants had complete medical history and had undergone thorough physical examination, including body mass index (BMI) assessment. Laboratory tests included serum total testosterone and glycated haemoglobin (HbA1c) measurements. Quantitative Androgen Deficiency in the Aging Male (qADAM) questionnaire scores were also recorded. Morning samples of total serum testosterone levels were assessed at three time points: baseline, 1 and 3 months.

Results

Testosterone levels increased at 1 and 3 months in all three groups. The mean baseline testosterone level was $2.31 \pm$

0.66 nmol/L, BMI was 30.8 ± 6.2 kg/m², and qADAM score was 20.5 ± 3.8 . Testosterone levels increased in all groups at all time points, with a final mean value of 5.17 ± 1.77 nmol/L (223% increase) with no statistically significant difference among the groups. qADAM scores had increased in all groups at 1 month (CC group: 6.36; hCG group: 5.08; CC + hCG group: 7.26) and at 3 months (CC group: 12.73; hCG group: 11.82; CC + hCG group: 15.13) with a significant difference in intergroup analysis for the CC + hCG group compared with the other two groups ($P < 0.01$).

Conclusions

All three treatments were equally effective in restoring testosterone levels. Single-agent CC is simple, cheap and may be used as treatment for hypogonadism when maintenance of fertility is desired. This approach seems to be as effective as either hCG alone or a combination of hCG and CC.

Keywords

hypogonadism, infertility, testosterone, clomiphene citrate, human chorionic gonadotropin

Introduction

Testosterone deficiency increases with age, with a reported annual decline in circulating testosterone levels of 0.4–2.0%. In middle-aged men, the incidence has been found to be 6%. Testosterone deficiency is more prevalent in older men, in those who are obese and have

comorbidities, and in men with poor health status [1]. Testosterone deficiency is also common in men who are seeking fertility treatment, with an incidence of 17% in men with obstructive azoospermia, 35% in men with normal semen analysis, 43% in men with oligospermia and 45% in men with non-obstructive azoospermia [1,2].

Testosterone deficiency may present with a variety of symptoms, such as decreased libido, fatigue, poor concentration, erectile dysfunction, lack of concentration and depressed mood; however, these symptoms are non-specific. Testosterone deficiency is also associated with multiple negative long-term systemic effects, including increased rate of cardiovascular disease, diabetes and bone density loss, as well as an increase in all-cause mortality [1,3]. The clinical diagnosis of testosterone deficiency is based on a combination of symptoms and signs, along with consistently low serum testosterone levels [1].

Testosterone therapy increases serum testosterone, with the aim of improving quality of life, well-being and, potentially, sexual function. The physical benefits may include a reduction in body mass index (BMI) and waist circumference, as well as improved glycaemic control [1,4–6].

The Androgen Deficiency in the Aging Male (ADAM) questionnaire, developed by Morley *et al.* [7], has been widely used as a screening tool for detecting men at risk of androgen deficiency since its development in 2000. Recently, the more detailed quantitative questionnaire, the qADAM, has been developed [8].

Despite being effective in the treatment of testosterone deficiency, exogenous testosterone is not suitable for those who are currently seeking fertility as it may impair spermatogenesis and even cause testicular atrophy, with subsequent exogenous testosterone dependency [8,9]. It has been suggested that spermatogenesis impairment caused by testosterone therapy is reversible; however, recent studies have shown that recovery may be partial and may take more than 1 year after testosterone therapy cessation [10,11].

Clomiphene citrate (CC), a selective oestrogen receptor modulator, is being used (off-label) for testosterone deficiency and has been shown not to interfere with spermatogenesis. It has been shown to be effective in increasing serum testosterone with few side effects in men with testosterone deficiency [9]. hCG injection is also considered to be an effective therapy in men with hypogonadotropic hypogonadism [12,13], but has rarely been studied in men with low testosterone and low to normal LH and FSH levels.

The standard therapy within our group of men's health clinics has been to use regular hCG injections for men seeking to improve testosterone levels while maintaining or improving fertility. CC has been used intermittently in selected patients. We were interested in the possible synergy of using both hCG and CC in these patients.

In the present trial, we studied men with symptomatic testosterone deficiency but who wished to preserve fertility, assessing the efficacy of a short course (3 months) of CC, hCG or a combined cycle of CC + hCG.

Material and Methods

The study was approved by the institutional ethics committee at our centre. In this prospective, multicentre randomized controlled trial, men with secondary testosterone deficiency (late-onset hypogonadism), willing to maintain their fertility, who met the following inclusion criteria were enrolled: low serum testosterone levels on at least two samples (3 ng/mL [300 ng/dL]; laboratory normal levels 3.1–8.6 ng/mL) and at least three positive symptoms from the qADAM questionnaire. Exclusion criteria were: primary testicular failure; hypogonadotropic hypogonadism; history of testosterone therapy; chromosomal abnormalities; and cryptorchidism history or a single testis. The men were randomized to one of the three treatment arms using a base 3 (1,2,3,2,1,3...) centralized random block allocation, according to the algorithm shown in Figure 1.

Primary Endpoint

The primary endpoint of the study was to compare the effectiveness of a short course (3 months) of either CC, hCG or a combined cycle of each therapy (CC ± hCG) in raising the blood testosterone level to physiological levels.

Secondary Endpoint

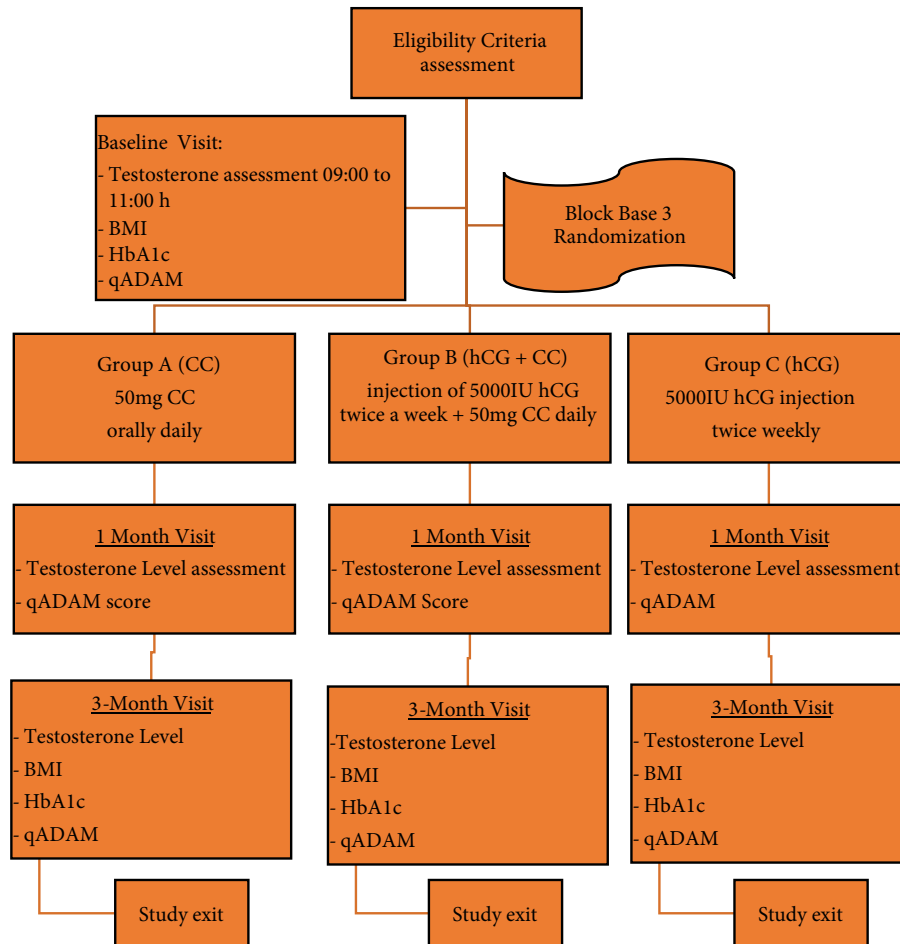
The secondary endpoint was to evaluate the impact of medical therapy on patients' symptoms using the qADAM questionnaire and on comorbidities (diabetes and obesity). Enrolled patients were then assigned to three different treatment groups (A, B and C) for a short course of therapy.

In Group A (CC group) the participants received 50 mg oral CC daily for 3 months. Group B (hCG + CC group) received a s.c. injection of 5000 IU of hCG twice weekly and 50 mg of CC daily for 3 months. Group C (hCG group) received 5000 IU of hCG by s.c. injection twice weekly for the same amount of time as the previous two groups. It is worth mentioning that all the treatments offered were entirely paid for by the participants. No open-label phase was offered after the study closure.

To assess the impact of therapy on comorbidities, two metrics were also measured: BMI and glycated haemoglobin (HbA1c). Testosterone levels were assayed, with blood samples taken between 9:00 and 11:00 hours at baseline, then at 1 and 3 months after the therapy. Blood samples for the groups taking hCG were planned to be taken 2 days after hCG injections. Testosterone levels were measured at baseline, and at 1 and 3 months after the therapy commencement, while HbA1c and BMI were measured at baseline and 3 months.

Because of the short follow-up, the qADAM questionnaire was used to better quantify the improvement in testosterone

Fig. 1 Study algorithm and visit schedule. CC, clomiphene citrate; HbA1c, glycated haemoglobin; qADAM, Quantitative Androgen Deficiency in the Aging Male scale.



deficiency symptoms. The only difference between the ADAM and qADAM questionnaires consists in the replacement of the 'yes/no' answers with a Likert scale of 1–5, where 5 represents absence of a given symptom and 1 represents the maximal symptom. The qADAM score ranges from 10 to 50, with a lower score indicating more severe symptoms [8]. All questions were weighted equally and no threshold score has been noted to accurately diagnose hypogonadism. Participants were assessed with qADAM questionnaires before commencing the therapy, at 1-and 3-month follow-ups.

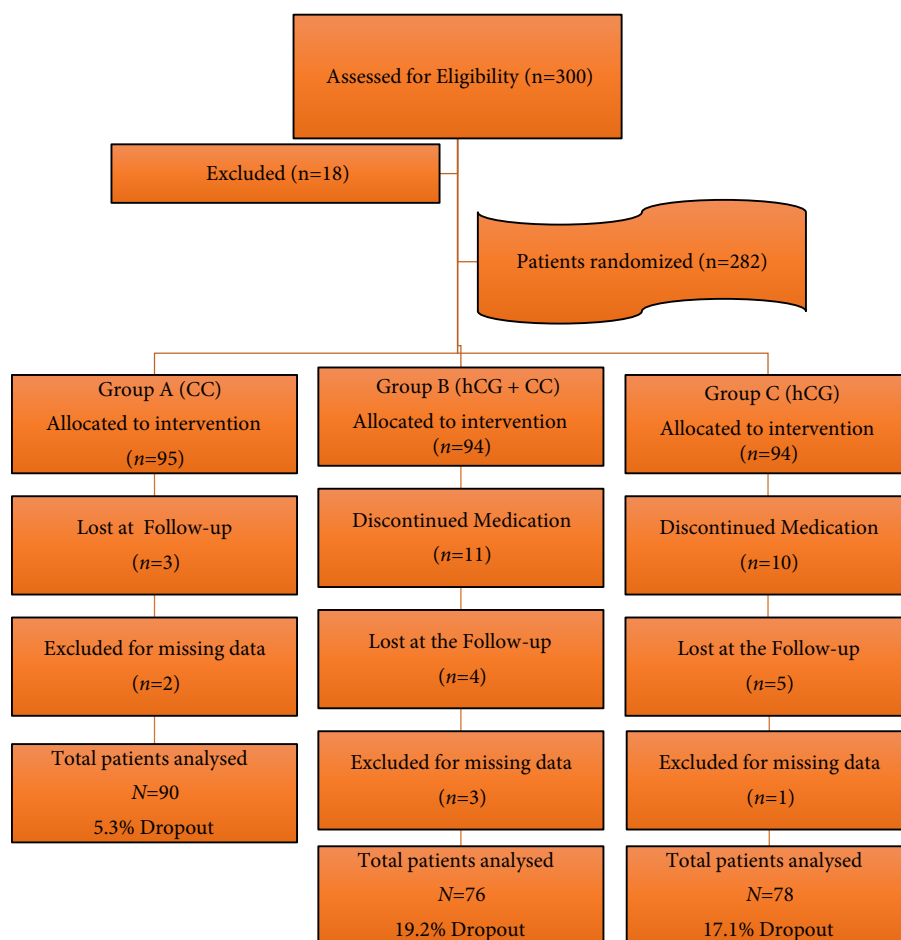
We performed a variance analysis (ANOVA) to detect statistically significant differences among the treatment arms at baseline and during the 3-month follow-up. Where a statistically significant difference was found *t*-tests were performed to assess which group differed from the others. SPSS (IBM SPSS Statistics for Macintosh Version 25.0, Armonk, NY, USA) and Microsoft Excel (Microsoft Corporation, Microsoft Excel for Mac 2016; Redmond, WA, USA) were used for statistical analysis.

Results

A total of 300 men were screened for eligibility criteria, 18 were excluded (6%), and 282 were randomized (Fig. 2). The baseline characteristics of the overall cohort were: mean age 41.8 ± 10.4 years; mean BMI 30.8 ± 6.2 kg/m² and mean HbA1c $6.5 \pm 1.9\%$. The mean serum testosterone level was 2.31 ± 0.66 nmol/L and the mean qADAM score was 20.5 ± 3.8 .

In all, 95 men were allocated to Group A (CC). Participants in this group received 50 mg oral CC daily for 3 months. Three men in this group were lost during the follow-up and two were excluded from statistical analysis for missing data. A total of 90 participants were analysed (94.7%).

A total of 94 men were allocated to Group B (hCG + CC) and received s.c. injection of 5000 IU hCG twice weekly and 50 mg CC daily. In this group, 11 men discontinued the therapy (11.7%), four were lost to follow-up (3.76%) and

Fig. 2 Treatment group composition and drop-out rates.

three were excluded from the statistical analysis for missing data (2.82%). A total of 76 men were included in the final analysis (71.44%).

In Group C (hCG), 94 men received 5000 IU of hCG by s.c. injection twice weekly. In this group 10 men abandoned the study before the end (9.4%), five were lost to follow-up (4.7%) and one man was excluded for missing data (0.94%). A total of 78 men were then analysed (84.96%).

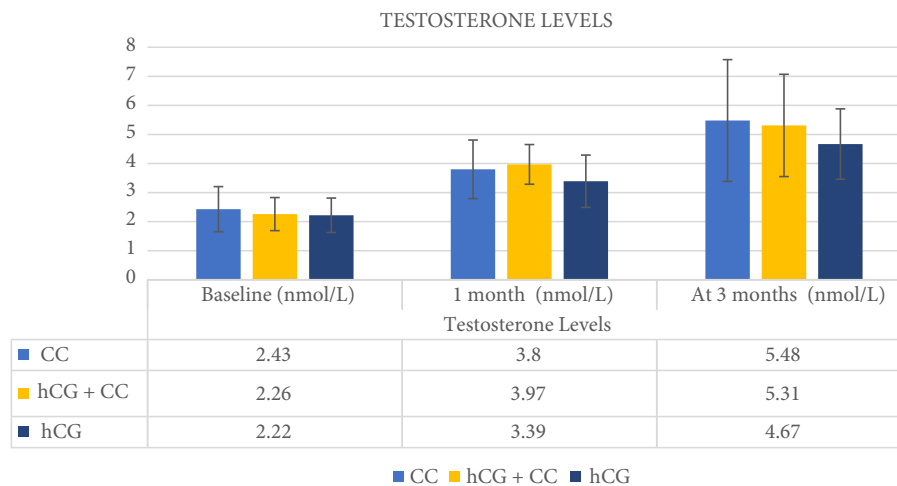
Testosterone

Testosterone levels increased significantly in all three groups (Fig. 3). Baseline serum testosterone levels were 2.43 ± 0.78 nmol/L, 2.26 ± 0.57 nmol/L and 2.22 ± 0.59 nmol/L for the CC, hCG + CC and hCG groups, respectively. No baseline statistical difference between them was found. At 3 months, testosterone level was highest in those in the CC group (5.48 ± 2.09 nmol/L), and lowest in the hCG group (4.67 ± 1.21 nmol/L).

Two statistically significant differences were noted in testosterone levels at 3 months (ANOVA *F* statistic 4.82, *F*-critical value 3.03; $P = 0.009$) between the CC and hCG groups ($P < 0.002$) and between the hCG + CC and hCG groups ($P < 0.002$). There was no significant difference between the CC group and the hCG + CC group ($P = 0.57$; Table 1). Changes in testosterone levels were measured for the following time intervals: 0–1, 1–3 and 0–3 months (Fig. 4).

At 1 month, the testosterone increase was greatest in the hCG + CC group (1.71 ± 0.67 nmol/L) and lowest in the hCG group (1.17 ± 0.74 nmol/L). A significant difference was found between the CC and the hCG + CC groups ($P < 0.007$) and between the hCG + CC and hCG groups ($P < 0.05$), but no difference was seen between the CC and hCG groups (Table 2).

Testosterone increase at 3 months was greatest in the hCG + CC group (3.05 ± 1.84 nmol/L) and lowest in the hCG group (2.45 ± 1.11 nmol/L). There was no statistically significant difference

Fig. 3 Mean testosterone levels of the 282 men enrolled in the study at baseline and at 1 month and 3 months. CC, clomiphene citrate.**Table 1** Results of the *t*-test performed on serum testosterone differential increase (0–1 month) at the end of the first month of follow-up.

Testosterone serum level difference from 0 to 1 month (<i>t</i> -test)		
	CC	hCG – CC
Mean	1.37	1.71
<i>t</i> statistic	–2.7536	
<i>P</i> (testosterone ≤ <i>t</i>) two-tailed test	0.007	
<i>t</i> critical value two-tailed test	1.9749	
	Difference	
	CC	hCG
Mean	1.37	1.17
<i>t</i> statistic	1.5484	
<i>P</i> (testosterone ≤ <i>t</i>) two-tailed test	0.123	
<i>t</i> critical value two-tailed test	1.9744	
	No difference	
	hCG – CC	hCG
Mean	1.71	1.17
<i>t</i> statistic	4.7631	
<i>P</i> (testosterone ≤ <i>t</i>) two-tailed test	4.4E-06	
<i>t</i> critical value two-tailed test	1.97580	
	Difference	

CC, clomiphene citrate. A statistically significant difference was found between the CC vs hCG + CC group and between HCG + CC vs HCG group.

between groups using ANOVA, and comparison *t*-tests were therefore not performed (ANOVA *F* statistic = 2.98, *F*-critical value = 3.03; *P* = 0.052). All groups showed a reduction in BMI at 3-month follow-up (Fig. 5), with the lowest BMI decrement in the hCG group (–1.19%) and the highest (–1.72%) in the combined therapy group; however, no significant difference was found among the three arms (ANOVA *F* statistic = 1.01, *F*-critical value = 0.36; *P* = 3.033).

Again, all three groups showed a statistically significant improvement in qADAM scores after 3 months, as would be expected with the increased testosterone levels. Intergroup analysis suggests a marginally higher qADAM score in the combination (hCG + CC) group compared with the hCG or

CC groups, but as this was an unblinded study we did not feel more detailed analysis of these data was clinically relevant.

Discussion

Physiological spermatogenesis depends on adequate gonadotrophin secretion with subsequent elevation in intra-testicular testosterone concentrations. Testosterone reversibly suppresses spermatogenesis by suppressing the pituitary secretion of LH and FSH. For this reason, androgens have been investigated for potential use in male medical contraception [14,15]. Despite this, a recent AUA survey showed that 25% of the responding urologists still used exogenous testosterone to treat idiopathic infertility. Surprisingly, a significant difference in practice patterns was seen between general urologists and andrology fellowship-trained urologists; general urologists were more likely to use testosterone than andrologists (*P* = 0.001) [16].

Although sperm parameters can return to normal after cessation of exogenous androgens, many authorities suggest that the various types of testosterone treatment are inappropriate in men wishing to preserve fertility [10,11,17,18].

Effects of CC are achieved by inhibiting the negative feedback of oestradiol to the hypothalamic–pituitary–gonadal axis at the level of the hypothalamus. This leads to release of LH and FSH from the anterior pituitary, which stimulates Leydig cells, leading to testosterone production. Published data suggest that CC may be an appropriate alternative treatment for male hypogonadism because it is safe, cheap and effective for improving serum testosterone levels [8,9], but only few randomized studies on this are currently available.

Ramasamy et al. [3] reported their results in a total of 93 men, who received testosterone injections (*n* = 31),

Fig. 4 Mean increase in testosterone serum level from 0 to 1, 1 to 3 and 0 to 3 months. The data shown are representative of the entire cohort of 282 men. CC, clomiphene citrate.

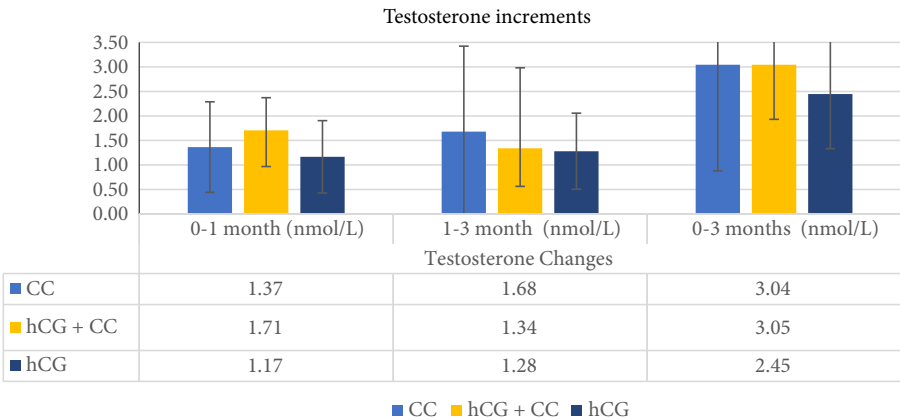


Table 2 Results of the *t*-test performed on the 3-month follow-up serum testosterone level data.

t-test testosterone at 3 months		
	CC	hCG – CC
Mean	5.48	5.31
t statistic	0.5557	
P (testosterone ≤ t) two-tailed test	0.579	
t critical value two-tailed test	1.9745	
	No difference	
	CC	hCG
Mean	5.48	4.67
t statistic	3.1036	
P (testosterone ≤ t) two-tailed test	0.002	
t critical value two-tailed test	1.9763	
	Difference	
	hCG – CC	hCG
Mean	5.31	4.67
t statistic	3.1036	
P (testosterone ≤ t) two-tailed test	0.002	
t Critical two-tailed test	1.9763	
	Difference	

A statistically significant different was found between the CC and the hCG group and between the hCG + CC and the hCG group.

testosterone gels (*n* = 31) or CC (*n* = 31) and who were were age-matched from a retrospective cohort of 1 150 men receiving testosterone supplementation therapy. They concluded that testosterone supplementation regimens and CC were efficacious for improving serum total testosterone levels. They also found that men on CC for symptomatic hypogonadism reported hypogonadal symptoms similar to those of age-matched men on testosterone injections and gels [3]. In another study by Da Ros *et al.* [19], CC was tested for effectiveness in restoring endogenous testosterone production. In that trial, 125 men with a mean age of 62 years were given 25 mg CC daily. Before treatment, all the men had either below-normal or low to normal testosterone levels and all complained of decreases in libido. The mean follow-up was 6 months. Post-treatment testosterone levels increased by a

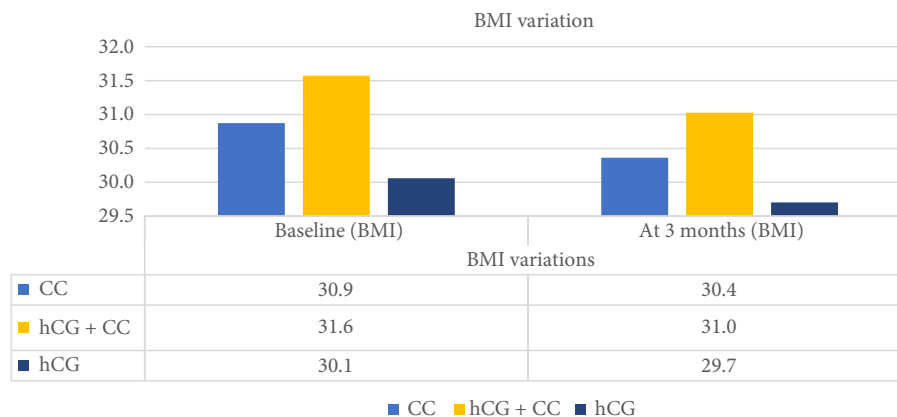
mean of 115%. The study concluded that CC should be considered as a therapy for men with hypogonadism [19].

Taylor and Levine [20] conducted a study in which CC gave rise to significant increases in testosterone levels from baseline values. These were similar to increases made in testosterone gel replacement therapy. A total of 104 men began CC (50 mg every other day) or testosterone gel replacement therapy (5 g of 1% gel). The mean follow-up was 23 months for CC and 46 months for testosterone gel replacement therapy. The mean post-treatment testosterone levels were 573 ng/dL (mean baseline 277 ng/dL) in the CC group and 553 ng/dL (mean baseline 221 ng/dL) in the testosterone gel replacement therapy group. The authors observed that the cost per month of CC was ~\$190 less than the cost of Testim® 1% (5 g daily), at \$270, and of AndroGel® 1% (5 g daily), at \$265. Compared with testosterone gel replacement therapy, CC was found to be a less expensive option for men with hypogonadism, representing efficacy with minor side effects [20].

The average 3-month course of CC in our country (Saudi Arabia) costs \$50.00. This is significantly cheaper than same course of testosterone (two long-acting injections; transdermal testosterone therapy is not available in our country [Saudi Arabia]), which costs \$300.

In the present study, we aimed to assess the efficacy of three alternative treatment options CC, hCG and combined therapy (CC + hCG) in increasing testosterone levels. Our interest in conducting this study was largely to see if adding CC to hCG treatment would give a benefit, with our null hypothesis effectively being that CC would add no benefit to hCG treatment in this group of men. In fact, the CC-only group, which we had intended to serve as a control, did as well as the other groups. Objectively, we found that CC, hCG + CC and hCG were all equally effective in restoring normal testosterone serum levels after 3 months; CC and hCG act

Fig. 5 The figure below shows the baseline average patients BMI measured at the enrolment (Baseline) and at 3 months.



differently on human body physiology but lead to analogous results.

In the present study the group treated with CC 50 mg daily had a steady rise in serum testosterone level from the first month until the end of the third month of follow-up. Of the 90 participants in this group, 84 (93.3%) achieved a physiological testosterone level (≥ 3 ng/mL) on CC by month 3, with a mean increase in testosterone from baseline of 225% (Δ testosterone 3.04 ng/mL).

The hormone hCG induces testosterone production by stimulating Leydig cells directly. Physiological serum levels can be achieved with a standard dosage of 1500–5000 IU administered i.m. or s.c. twice weekly. In patients with secondary hypogonadism and fertility issues, and in selected cases of primary hypogonadism, hCG treatment can be chosen to support endogenous testosterone production for the period of infertility treatment. The dosage must be individually adjusted to prevent serum FSH level suppression [21].

Therapy with hCG therapy (recombinant hCG) is traditionally used in men with hypogonadism desiring fertility because it shares a receptor with LH and produces similar effects. The dose is usually titrated to a serum testosterone concentration in the mid- to normal range [22]. Kobori et al. [23] reported both successful improvement in chemistry (increase in serum testosterone) and symptoms in seven men (aged 34–45 years) with azoospermia and/or sexual dysfunction, with a low serum testosterone concentration after using hCG 5000 twice weekly [23].

Costing approximately US\$260, hCG treatment is more expensive than CC. In the present study, men treated with hCG experienced a steady increase in testosterone levels to within the normal range with a dose of 5000 IU hCG twice weekly, from the first month until the end of follow-up. Of 78 participants, 71 (91%) achieved a physiological

testosterone level by month 3, with a mean change from baseline of 210% (Δ testosterone 2.45 ng/mL).

In men who were treated with the combination therapy (hCG + CC), mean serum testosterone levels rose to within the normal range within 1 month of starting the medication, and continued to rise gradually over the entire follow-up. Of 76 participants, 75 (98.7%) achieved a physiological testosterone level on hCG + CC by month 3 for a mean change from baseline of 235% (Δ testosterone 3.05 ng/mL). None of the treatments were superior to another, however, with regard to androgen stimulation.

It is worth mentioning that there were higher discontinuation rates in the hCG + CC and hCG groups than in the CC group; 11, 10 and three participants dropped out of the study, respectively. In the hCG group, 80% attributed their drop-out to intolerance of twice weekly injections. The remaining participants left because of the higher treatment costs (all participants in this study were paying the full cost of their treatment).

The participants in the present study experienced a significant BMI reduction of $\sim 1.5\%$. Again, no statistically significant differences in efficacy were seen among the treatments offered. We were unable to show significant changes in either qADAM scores or HbA1c values. Patients were instructed to stick to their usual lifestyle (activities, diet) during the 3-month treatment course to ensure that there would be no other factors that might influence the outcome.

The main limitation of the present study was the randomization methodology used. Statistical power was calculated, expecting a difference of 10% in serum testosterone with 95% confidence; the groups were expected to include 92 evaluable participants each.

Participants were randomized, using a base 3 block randomization scheme and centralized random number

generator. This approach might have had an impact on the statistical power of the study because, theoretically, the next randomization would not have been totally blind; however, the central allocation of treatment in a rotating fashion should have meant this would be unlikely.

We observed a heterogeneous drop-out rate among the three groups. The hCG + CC group and the hCG group had higher rates than the CC group. In the former two groups, 19.2% and 17.1% of participants, respectively, dropped out, whereas in the CC group the rate was only 5.3% (1/20 participants). The participants who dropped out of the CC group might have had different reasons, such as side effects and costs. The latter was an extremely important factor over the course of the trial. The study was not funded, therefore, all participants had to cover the costs of their own therapy. This is also the reason why follow-up was restricted to 3 months only.

As can also be seen from our data, qADAM and HbA1c variables were not analysed because these were found to be heterogeneous at the baseline analysis. This might have been the result of an imperfect randomization method or an underpowered sample.

In addition, we did not stratify participants according to gonadotrophin levels. All participants had late-onset hypogonadism with normal LH and FSH levels, and the majority presented seeking either fertility or erectile dysfunction advice. It may be that men in our region (Middle East) have expectations of continuing fertility in middle age and beyond, expectations which are not seen in most western countries. Stratifying by low, normal or high gonadotrophin levels may have yielded different results but would have made the study unmanageable in our clinical network because of a much greater number of participants.

Lastly, we did not compare our treatment groups with the standard of care, testosterone. This was not possible because all the enrolled participants wished to maintain their fertility; if we had created a fourth testosterone treatment group, the enrolment criteria would have been different, making it non-comparable with the other groups.

In conclusion, CC alone may be an option for men with hypogonadism when maintenance of fertility is desired. Published data show that CC is a safe and efficacious drug to use as an alternative to exogenous testosterone [9,19] and our data suggest it is as effective in this patient group as either hCG alone or a combination of hCG and CC. While not directly compared in the present study, our results show testosterone improvements similar to those seen with full exogenous testosterone replacement therapy. In short-term use, CC is a safe treatment option for men with hypogonadism, demonstrating biochemical and clinical efficacy. It should be discussed with all men who have low testosterone and who wish to retain their fertility.

Conflict of Interest

None of the Authors involved into the study has conflict of interest to declare.

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Abbreviations: BMI, body mass index; CC, clomiphene citrate; HbA1c, glycated haemoglobin; qADAM, Quantitative Androgen Deficiency in the Aging Male scale.