1. Introduction

Male hypogonadism, referred to also as testosterone deficiency, is a medical problem highly prevalent in the middle- and old-aged male populations. Approximately 20–30% of men in this population were considered testosterone deficient according to various studies, which may be affected by aging and other comorbidities such as cardiovascular disease, diabetes, obesity, and metabolic syndrome. Benefits of testosterone replacement therapy are clearly established for sexual function, increase in lean muscle mass and strength, mood and cognitive function, and a possible reduction in frailty and osteoporosis. However, exogenous testosterone replacement causes suppression of the hypothalamic–pituitary–gonadal axis via a negative feedback mechanism, which may lead to diminished testicular size and consistency, and ultimately, infertility. This could be a great concern in hypogonadal men who require exogenous testosterone replacement but also wish to remain fertile.

Clomiphene citrate (CC) is a selective estrogen receptor modulator that increases gonadotropin levels and consequently stimulates testosterone and sperm production. CC may be used as an alternative treatment for patients with hypogonadism when maintenance of fertility is desired; however, limited publications have demonstrated its treatment efficacy, especially in the Asian population. In this study, we investigated the efficacy of CC in the treatment of hypogonadism, with the objectives of assessing the increase in endogenous serum testosterone and evaluating the patients’ subjective improvement of symptoms.

2. Materials and methods

We retrospectively reviewed the patients diagnosed with hypogonadism who received CC in our center in 2015. Hypogonadism is defined as a low serum testosterone (< 300 ng/dL) and requires the patient presenting with symptoms of hypogonadism. For patients who wish to receive testosterone replacement but also desire fertility, CC is offered as an alternative treatment. However, due to lack of safety information on CC use in patients contraindicated to testosterone replacement therapy, patients with concerns of pre-existing prostate cancer, significant erythrocytosis, untreated obstructive sleep apnea, and untreated severe congestive heart failure were excluded from receiving CC treatment. CC was offered at the patient’s discretion after having extensive discussion with the treating urologist regarding the available treatment options and their risks. For those who decided to receive CC treatment, each patient was treated with a daily dose of 50 mg CC. The patients were evaluated after at least 3 weeks of CC administration for serum testosterone levels. The Androgen Deficiency in Aging Males questionnaire was administered before treatment and during follow up for subjective outcome measures. The patients were monitored for side effects, in a similar manner to patients receiving testosterone replacement therapy, and were recorded respectively.
Patients who received testosterone replacement therapy within 90 days before CC was initiated were excluded from our analysis.

Statistical analysis was performed using SPSS (IBM SPSS Statistics Version 20), with p values < 0.05 considered statistically significant. Mean and standard deviation of the studied variables were reported. Wilcoxon signed-rank test was used to compare the pretreatment and post-treatment serum testosterone level and other variables. We used Mann–Whitney U test to compare the mean serum testosterone change between different patient groups in our subgroup analysis.

Our study obtained ethical approval from our local institutional review board.

3. Results

A total of 15 patients with hypogonadism were treated with CC in our center in 2015. The post-treatment serum testosterone level was not available in five patients, who were excluded from our analysis. Ten patients completed post-treatment evaluation and were included for analysis. The mean age of our patients was 50.5 ± 12.5 years. Our patients were generally healthy without significant medical comorbidities, with the exception of one patient with underlying hypertension and diabetes mellitus, and another patient with hyperlipidemia. All patients had at least one symptom suggestive of hypogonadism. Erectile dysfunction was the most presented symptom, which was seen in all 10 (100%) patients. Other hypogonadal symptoms included decreased libido in eight (80%) patients, general malaise in five (50%) patients, and infertility in two (20%) patients (Table 1).

Mean pretreatment serum testosterone level was 246 ± 76 ng/dL. After a treatment interval ranging from 20 days to 193 days, the mean post-treatment serum testosterone level increased to 548 ± 281 ng/dL, which was statistically significant (p < 0.01; Figure 1). The number of successfully treated patients with target serum testosterone level reaching ≥ 400 ng/dL was eight patients (80%). Within 35 days, six (60%) patients had reached the target serum testosterone level. Of the two men whose treatment failed, one 64-year-old patient had an initial testosterone level of 60 ng/dL, which was profoundly low compared with the average of patients in our study, with no change noted after CC treatment for 2 months. Serum testosterone level improvement from 248 ng/dL to 336 ng/dL was noted in the other 50-year-old patient, although this did not reach the target treatment level.

Patient subjective treatment response was evaluated using the Androgen Deficiency in Aging Males questionnaire. The mean number of positive answers from the 10-question questionnaire was 5.9 ± 1.9 before CC treatment, and improved to 1.7 ± 1.1 after treatment, which was, however, statistically insignificant (p = 0.10). There were no side effects reported during the entire treatment course.

We performed a subgroup analysis of our patients, where the patients aged ≥ 50 years were compared with the patients aged < 50 years for treatment efficacy of CC. The mean serum testosterone change after CC treatment was 198 ± 174 ng/dL in the older patient group, compared with 455 ± 255 ng/dL in the younger patient group, which was statistically insignificant (p = 0.08; not included in Table 1).

4. Discussion

Hypogonadism consists of a variety of nonspecific symptoms including decreased libido, fatigue, poor concentration, erectile dysfunction, lack of concentration and depressed mood, which could often be unnoticed by patients or treating physician, making the diagnosis particularly difficult. This underdiagnosed and undertreated medical condition is associated with obesity, insulin resistance, and an adverse lipid profile in men, and is independently associated with increased all-cause and cardiovascular mortality. The prevalence of hypogonadism is related to aging. Because the Taiwanese population represents an aging society with continued increase of life expectancy, the impact of this medical condition will be increasingly important. Testosterone replacement is the current mainstay treatment, with well-established benefits to the quality of life of men in middle and old age, especially in terms of body composition, muscle, and bone.

Despite higher prevalence in the elderly population, hypogonadism may also affect younger patients. For these younger patients of reproductive age, testosterone replacement therapy may greatly compromise their fertility because of downregulation of gonadotropins causing diminished testicular size and function. Although this subinfertility condition is often reversible after cessation of exogenous testosterone supplement, it is still worrisome for those patients who remain interested in fertility.

CC is a selective estrogen receptor modulator that could indirectly increase serum testosterone by competing with estradiol at...
the hypothalamic level, and then results in inhibition of the negative feedback for gonadotropin release. While CC is not Food and Drug Administration approved for hypogonadism, it has been used off label for many years.\textsuperscript{10,11} Although only a limited number of relevant publications without a strong level of evidence exist, most have shown efficacious treatment of CC in hypogonadal men. In a cohort of 86 young patients with mean age 29 years, Katz et al\textsuperscript{10} showed significant improvement in serum testosterone level and subjective responses after CC. Taylor and Levine\textsuperscript{12} compared patients receiving CC (65 patients) and testosterone gel replacement therapy (39 patients) and demonstrated equal efficacy, with lower cost in the CC group. However, their average patient age was 42 years (CC) versus 57 years (testosterone gel). Ramasamy et al\textsuperscript{11} compared 93 hypogonadal men on testosterone injections or gels or CC, and found that the post-treatment median serum total testosterone level in men on CC was lower than in men receiving testosterone injections but similar to that in men on testosterone gels. The median age in all groups was 40–44 years. Moskovic et al\textsuperscript{13} followed up 46 patients for 3 years and demonstrated the long-term safety and efficacy of CC. Although promising results of CC treatment in hypogonadal men were shown in the aforementioned studies, these studies did not demonstrate the use of CC in more elderly populations.

In a previous study including older patients, Tenover et al\textsuperscript{14} compared 1 week of CC therapy in younger (22–35 years) and older (65–84 years) patients, and reported that the elderly group had significantly lower serum total testosterone and non-SHGBound (bioavailable) testosterone levels than did younger men. However, due to the small patient number (29 patients and 26 patients in each group) and the more extreme age in the older patient group (>65 years), the efficacy of CC in the older population remains inconclusive.

In our study, eight (80%) patients reached the target serum testosterone level of >400 ng/dL after CC treatment, with a mean serum testosterone level increase from 246 ± 76 ng/dL to 548 ± 281 ng/dL. We have shown treatment results (including safety and efficacy) comparable with the earlier studies, however, our mean patient age was 50.5 years, showing the efficacy of CC in the older cohort of patients. Furthermore, to our knowledge, this is the first study describing the treatment results of CC in Asian hypogonadal men. We have demonstrated the rapid treatment effect of CC, with most patients (60%) in our study cohort reaching target serum testosterone level within 35 days, whereas the remaining patients did not demonstrate this rapid treatment effect due to different follow-up protocols for serum testosterone. The average expense of drug treatment for patients who received CC in our study was NTD180/mo, which is much lower than for patients receiving exogenous testosterone replacement therapy. Due to the overall benefit of high efficacy, low adverse events, and low cost, CC could even be suggested as an initial treatment for hypogonadal patients.

Our limitations include the small patient cohort of our study, and its single-armed and retrospective nature. Clinical information such as body mass index or waist circumference were not available in our study; therefore we could not demonstrate the influence of obesity on our treatment results. Furthermore, some important laboratory value changes, such as prostate-specific antigen and hematocrit levels before and after CC treatment, were not included in our analysis due to the retrospective nature of this study. Pretreatment testicular volumes and luteinizing hormone levels have been shown in a previous study as factors predictive of CC treatment response in hypogonadal men,\textsuperscript{15} where patients with low pretreatment testicular volumes and high luteinizing hormone levels had a lower success rate from CC treatment, which suggests that patients with primary testicular failure could not benefit well from CC treatment. However, we did not routinely screen our patients for primary testicular failure features before initiating CC treatment, therefore this study was unable to demonstrate the different treatment results in patients with different primary causes of hypogonadism.

5. Conclusion

In conclusion, CC is a safe and effective alternative treatment for hypogonadal men, which has a role for those unable to receive testosterone replacement therapy due to concerns of infertility.

Conflicts of interest

All authors have no conflicts of interest to declare.

References


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