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Treatment of male hypogonadism with clomiphene citrate: Review article

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Abstract

Clomiphene citrate (CC) is a selective estrogen receptor modulator and estrogen antagonist originally developed in 1956 and introduced into clinical medicine in 1967 for the treatment of female infertility [1]. CC has also been explored for off-label use for male infertility and male hypogonadal symptoms [1]. This article will review the medical literature on CC and its contribution to the treatment of male hypogonadism. A comprehensive review of the literature pertaining to CC through April 2022 was performed through PubMed. We looked at variety of questionnaires for hypogonadal men and our goal was to define the role of Clomiphene Citrate in treatment of male secondary hypogonadism with structurally intact hypothalamic- hypophyseal axis (HT-HP), but physiologically changed and compare it with the currently FDA approved treatment with Testosterone in different forms. We included 30- articles relevant to CC. CC can increase the Testosterone as much as Testosterone gel in hypogonadal patient with the similar improvement of the hypogonadal symptoms while preserving fertility and sperm production in males with secondary/tertiary hypogonadism and structurally intact HT-HP axis [2,3]. Also, the safety of CC was discussed in our article and it was compared to Testosterone safety as well, while treating men with secondary/tertiary hypogonadism with CC and structurally intact hypothalamic- hypophyseal axis, but physiologically changed. CC is regarded as an effective therapy for specific patients who suffer from male factor infertility and complain of hypogonadal symptoms. More studies are needed to further validate CC's efficacy for male infertility and hypogonadism [1].

Keywords: Clomiphene Citrate (CC); Testosterone; Hypogonadism; Polycythemia; Infertility

1. Introduction

Hypogonadism is a common medical condition among men. Hypogonadism is a clinical and biochemical testosterone insufficiency syndrome, affecting various organ functions and quality of life, according to the European Association of Urology. Common symptoms of hypogonadism are erectile dysfunction, reduced sexual activity and desire, decreased morning erections, mood changes, and loss of muscle strength among others. The prevalence for symptomatic hypogonadism at age 40–79 years, varies between 2.1% and 13% and increases with age and presence of obesity, cardiovascular disease, chronic obstructive pulmonary disease (COPD), diabetes mellitus (DM) type 2, human immunodeficiency virus (HIV), chronic kidney disease, malignancies, obstructive sleep apnea, cirrhosis of the liver, pituitary tumors, hyperprolactinemia, many medications among others. Low testosterone level is also a sign of poor general health [4,5].

Causes of hypogonadism can be classified based on disruptions at various levels of the hypothalamic–pituitary–gonad (HT-HP-G) axis. Primary hypogonadism is the most frequent cause of hypogonadism, resulting in low serum testosterone concentration and high serum gonadotropin concentration. Primary hypogonadism results from direct

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testicular failure; the most common reasons are Klinefelter syndrome, Chemotherapy, mumps, Radiation therapy to the testes and testicular tumors.

On the contrary, in secondary/tertiary hypogonadism the testes are intact, but inadequately stimulated by gonadotropins, resulting in hypogonadism, usually with reduced or inappropriately normal serum concentration of gonadotropins. Reasons for secondary/tertiary hypogonadism are, for example, hyperprolactinemia, Kallmann's syndrome, and obesity, obstructive sleep apnea, medications, hemochromatosis among others [4]. Adult-onset hypogonadism or late-onset hypogonadism, is a symptomatic testosterone deficiency in middle-aged and older men-androgen deficiency in aging male (ADAM), with normal HPG-axis function [4,5].

Testosterone therapy (TTh) is the first-choice treatment for men with hypogonadism [6]. The goal of this treatment is to increase serum testosterone and restore androgen-dependent functions, for example, muscle mass and strength, sexual function, libido, bone density, and general well-being. However, TTh has some notable side effects. The most common side effect in older men is polycythemia and in younger acne [6]. Subfertility is one of the most crucial side effects of TTh, especially for men with an active or possible future child wish, because endogenous testosterone is reduced by negative feedback on HT-HP axis [1].

Other side effects are, for example, increase in prostate volume, increase in prostate specific antigen (PSA), elevated hematocrit (Ht), serum estrogen concentration and serum lipid alterations as well as worsening of the obstructive sleep apnea [6].

Preserving fertility and costs are important reasons not to prescribe TTh for men with hypogonadism.

Other medications used for secondary/tertiary hypogonadism are human chorionic gonadotropin (hCG) and selective estrogen/androgen receptor modulators (SERMS and SARMS) [7].

Clomiphene citrate (CC) is a SERM occupying estrogen receptors in the hypothalamus and pituitary gland leading to gonadotropin release, which leads to increased testicular stimulation and testosterone production. CC has been used since 1960 for ovulation induction in women. It has been used off-label for men with hypogonadism.

The US Food and Drug Administration (FDA) did not approve the medicine, because of unclear effectiveness.

CC is widely used in the medical practice for men with secondary / tertiary hypogonadism with intact HT-HP axis, but physiologically changed who want to preserve their fertility [1].

2. Mechanism of Action of Clomiphene Citrate

The HT-HP-Gonad/HT-HP-G/ axis in males includes the hypothalamus, the anterior pituitary gland, and the testicles. Gonadotropin-releasing hormone (GnRH) is produced from the hypothalamus, which stimulates the production of LH and FSH in the anterior pituitary gland. LH and FSH released from the anterior pituitary promote the production of testosterone and spermatogenesis. Testosterone is then converted to estradiol by the aromatase enzymes. Estradiol in the normal physiological state exhibits part of the negative feedback mechanism on the reproductive axis by binding to the hypothalamus, which inhibits the continuous release of GnRH. CC competes with estradiol at the hypothalamic receptor level, specifically located on the anterior hypothalamus and hypophyseal gland, , which blocks the negative feedback mechanism and results in increased GnRH and gonadotropins- LH and FSH.. CC has a half-life of 5 days and is an isomer that consists of two compounds, 38% zuclomiphene (cis-isomer) and 62% enclomiphene, which are both excreted through the intestines. Zuclomiphene is both a partial estrogen agonist and estrogen antagonist, whereas enclomiphene is completely antiestrogenic. Unlike testosterone, both compounds do not suppress the HPG axis, but actually lead to an increase of LH and FSH, which results in an increased production of intratesticular testosterone by the Leydig cells and the promotion of spermatogenesis [1].

Enclomiphene alone, which is a pure estrogen antagonism unlike the combination in CC, has also been investigated as a therapeutic alternative to treat hypogonadism. Wiehle et al. evaluated its effectiveness on spermatogenesis and documented that all of the hypogonadal patients treated with enclomiphene 25 mg daily remained normospermic by the end of treatment [1].

A prospective study revealed an increase in the T:E ratios by 60.9% at 12 weeks of 25 mg daily of CC treatment, with a more significant rise in T: E in ≥40-year-old men when compared with those <40 years old [1].

3. Clomiphene citrate use in men with Hypogonadism

In a recent study by Da Ros et.al. Clomiphene citrate was tested for effectiveness in restoring endogenous testosterone production. In these trial, 125 men with an average age of 62 years were given clomiphene citrate (25 mg daily). Before the treatment, all men had either below normal or low normal testosterone levels and secondary hypogonadism. Moreover, all patients complained from decreased libido. The average follow up was 6 months. After treatment total testosterone levels increased by an average of 115%. The study concluded that clomiphene citrate should be considered as a therapy for male patients with secondary/tertiary hypogonadism and structurally intact HT/HP axis [8].

Taylor et al. conducted a study in which CC significantly increases total testosterone levels from baseline values in secondary/tertiary hypogonadism and structurally intact HT/HP axis. The increment of the total testosterone was similar to the increment by testosterone gel replacement therapy (TGRT). One hundred and four men began CC (50 mg every other day) or TGRT (5 gm of 1% gel). The average follow up was 23 months for CC or 46 months for TGRT. Average post-treatment total testosterone levels were 573 ng/dL (average baseline 277 ng/dL) in the CC group and 553 ng/dL (average baseline 221 ng/dL) in the TGRT group. The increment of the total testosterone levels was similar between CC treated hypogonadal men and testosterone gel treated men. The authors observed that the cost per month of CC was about $190 less than the cost of testosterone gels -Testim® 1% (5 gm daily) at $270 and Androgel® 1% (5 gm daily) at $265. Compared with TGRT, CC demonstrates a less expensive option for men with hypogonadism, representing efficacy with minor side effects [9].

A similar study on clomiphene was performed by Moskovic et al. where forty-six hypogonadal males with secondary/tertiary hypogonadism and structurally intact HT/HP axis with an average age of 44 years were treated with clomiphene citrate for more than 12 months. The main outcome measured were long-term results of clomiphene treatment on hypogonadal males and predictors of response. Average baseline serum Total testosterone (TT) levels were 228 ng/dL. Post-treatment serum TT levels were 612 ng/dL, 562 ng/dL, and 582 ng/dL after 1, 2, and 3 years, respectively of treatment with CC. Patients were also given the Androgen Deficiency in Aging Males (ADAM) questionnaire. The ADAM score measured by ADAM questionnaire improved also. This investigation concluded that CC is effective as a long-term therapy for men with symptomatic secondary/tertiary hypogonadism and structurally intact HT/HP axis. In addition, CC can improve many of the ADAM symptoms [10].

In an earlier study from the same institution, Katz et al. concluded that long-term use of CC improved serum TT levels to normal in a safe and effective manner. In this analysis, eighty-six men between 22 and 37 years old with secondary/tertiary hypogonadism and structurally intact HT/HP axis with TT levels < 300 ng/dL) were assessed and treated for an average of 19 months. The participating men were started on CC 25 mg every other day. They were then titrated to 50 mg every other day. 550 ng/dL was the goal testosterone level. Once this total TT levels were reached, total testosterone/gonadotropin levels were measured biannually. With regards to scores on the Androgen Deficiency in Aging Males (ADAM) questionnaire, improvement was noted in each area excluding loss of height. Five of the ten variables saw significant improvement including feeling sad/grumpy, lack of energy, decreased life enjoyment, decreased libido, and decreased sports performance. This study demonstrates that CC is both an effective and safe testosterone therapy substitute in hypogonadal men with secondary/tertiary hypogonadism and structurally intact HT/HP axis [11].

Androxal®, or enclomiphene citrate, is the trans-isomer of clomiphene citrate [1]. Enclomiphene citrate is currently completing phase III clinical trials in the United States and may in the future be another alternative treatment to testosterone therapies. In a randomized study by Kaminetsky et al., the investigators compared levels of TT, FSH, and LH after hypogonadal males with secondary/tertiary hypogonadism and structurally intact HT/HP axis used either oral enclomiphene citrate or testosterone gel. Twelve male subjects were assigned to either of the two treatments. At baseline, the average testosterone level for all patients was 165 ± 66 pg/dL. Treatment with both enclomiphene citrate and testosterone gel raised total serum testosterone levels/TT/ back to the normal range. Both groups had about the same serum TT levels after 3- months and 6- months of therapy. After 6 -months, serum TT levels were 525 ± 256 pg/dL for enclomiphene and 545 ± 268 pg/dL for testosterone gel. The distinguishing factors between these two treatments were their FSH and LH levels as well as their sperm counts. Only enclomiphene citrate was associated with rise in FSH and LH as well as sperm counts. All of the enclomiphene citrate subjects had sperm counts above 75 million/mL, with an average sperm count of 176 million/mL. In contrast, the testosterone gel subjects did not surpass sperm counts of more than 12 million/mL. These findings were also evident throughout the follow-up period. This study suggests that enclomiphene citrate may prove to be a superior treatment as it is effective in increasing testosterone as well as sperm counts. The rise in FSH and LH levels could also point towards a shift back to normal endogenous testosterone production [12].

Wiehle et al. carried out another study for enclomiphene citrate. This randomized study also compared the effects of enclomiphene (Androxal®) *vs* AndroGel®, a transdermal testosterone gel. Enclomiphene citrate was given in three different doses: 6.25 mg, 12.5 mg and 25 mg Androxal®. Forty-four men with total testosterone levels less than 350 ng/dL at baseline were included in the study. Their average age was 53 years. After six weeks of treatment, patients who took 25 mg enclomiphene citrate had an average Total testosterone level of 604 ± 160 ng/dL while patients on the transdermal testosterone gel had an average total testosterone level of 500 ± 278 ng/dL. While these results were almost equivalent, AndroGel® patients saw a decrease in FSH and LH levels whereas enclomiphene citrate patients saw an increase levels. These outcomes correlate with the results of the aforementioned study. This study concluded that enclomiphene citrate was capable of increasing serum TT, FSH and LH levels in patients with secondary/tertiary hypogonadism and structurally intact HT/HP axis [2].

Not all the study confirmed the equal improvement of hypogonadal symptoms while using Clomiphene citrate versus Testosterone. In a study conducted by Pranav Dadhich at al. CC was compared to Testosterone injections or gel in 52- men with symptomatic secondar/tertiary hypogonadism and structurally intact HT/HP axis. Total testosterone increased from 281 ng/dl to 541 ng/dl on patients using testosterone injections or gel and from 235 ng/dl to 438 ng/dl in patients using CC. Men taking Testosterone injections or gel had in this study better improvement of hypogonadal symptoms measured by ADAM score and ADAM score for libido was significantly lower following the treatment with CC [13].

The association between hypogonadal symptoms and serum testosterone levels has been well documented. The previous investigation by the European Male Aging Study group delineated a significant inverse correlation between serum testosterone levels and the presence of poor morning erections, low sexual desire, and erectile dysfunction.

The results of this study shows that even though patients prescribed CC had an improved overall ADAM score, patients reported a significant decrease in libido. The etiology of this CC effect on libido has not been fully elucidated, but it is theorized that modulation of the estrogen receptor could have negative effects on libido. Estrogen, despite widely considered a “female” hormone, remains important to maintain libido in men [13]. However, modulation of the estrogen receptor by CC can impair estrogen's action and subsequently cause impaired sex drive [13]. Although CC is effective in improving overall hypogonadal symptoms, CC appeared, in this study, to negatively affect libido. Larger studies are needed to validate the effect of CC on libido.

The quantitative ADAM (qADAM) questionnaire was developed in 2010 to provide numerical values to the original ADAM questionnaire [1]. A higher numerical score was associated with lower likelihood of hypogonadal symptoms when compared to total testosterone. The qADAM score also had a positive correlation with total testosterone. Dadhich et al. evaluated changes in hypogonadal symptoms after 3 months of receiving CC or TRT, and observed a significant improvement in qADAM scores in both the CC and TRT group [1].

In a study by Peter Schlegel et al. long-term CC treatment of male hypogonadism in which 280 patients received CC for 3- years or longer and 120- patients received CC more than 3- years 88% achieved eugonadism and 77% reported improvement of symptoms of hypogonadism.

Considering the duration of CC therapy, the total follow-up differed between the studies included from 1.5-52 months after achieving total testosterone concentration goal between 400 to 700 ng/dl. Most studies described showed un effective response in the first month of treatment of hypogonadism with CC. CC challenge test supports this, where total testosterone after 7- days of treatment reached above 400 ng/dl and after 10- days above 500 ng/dl. The optimal effect of CC is seen after 90-108 days usually. The usual dose in majority of the studies of CC was between 25 mg, 50 mg or 100 mg every other day to 25 and 50 mg a day. Lower dose was associate with less side effects. There was a sustained response of serum total testosterone concentration after 24-52 months of usage in patients with secondary/tertiary hypogonadism and structurally intact HT/HP axis [4,14,15,16,17,18].

4. Adverse effects

CC is generally regarded by investigators to be well tolerated drug in the clinical practice [19]. There have not been many studies investigating the adverse effects of CC in men, especially in comparison with TRT. Most studies reported no major side effects of CC while investigating its efficacy. Side effects reported with CC treatment include headache, breast tenderness, fatigue, abdominal /pelvic pain, flushing, visual disturbances, dizziness, and mood instability which were found in 4-11% of patient [4].

When compared with TRT in a multi-institutional retrospective study of 363 patients, Wheeler et al. noted that CC had lower prevalence of secondary polycythemia than TRT (1.7% compared with 11.2%); no men in the CC arm had a hematocrit high enough to necessitate phlebotomy [20]. In their study of 104 men, Taylor and Levine investigated the long-term safety and efficacy of CC versus testosterone gel and noted that CC did not significantly increase cholesterol, PSA, or hemoglobin.

Chandrapal et al. reported no effect of CC on PSA and hematocrit in their study of 77 patients on CC [1].

Two cases reported switching TRT to CC in a patient with secondary polycythemia on TRT. These patients did not subsequently exhibit polycythemia on CC. One of the patients while receiving Testosterone therapy had polycythemia and TIA's, but after the switch from Testosterone replacement therapy to CC his HCT normalized and he did not have any more TIA symptoms {21,22].

Recently, Kavoussi et al. investigated the risk of deep vein thrombosis (DVT) in 1180 hypogonadal men either on TRT or CC and reported that only 1 out of 486 patients on CC developed DVT compared with 9 out of 694 patients on TRT [1].

In a prospective study of 125 hypogonadal men on CC, Da Ros and Averbeck did not find statistically significant differences when comparing pre- and post-treatment high-density -cholesterol, triglycerides, fasting plasma glucose, and prolactin levels. These studies highlight the safety of CC, especially compared with TRT regarding secondary polycythemia and DVT risks as well as metabolic risks [1].

5. Discussion

Clomiphene citrate is regarded as a useful treatment for men who suffer from secondary/tertiary hypogonadism with structurally intact HT-HP axis which have some physiological change of it and who desire fertility although not FDA approved, because of inconsistency of the data [23,24,25}

The drug leads to increase of total Testosterone (TT), the Free Testosterone (FT), LH, FSH, and estradiol

The ratio Testosterone/estradiol increases [26]. These elevations of testosterone and gonadotrophins show that CC is effective in improving endogenous testosterone secretion by stimulating the HT-HP-G-axis in men with secondary/tertiary hypogonadism and structurally intact HT/HP axis. During CC treatment, serum TT achieved the reference value of 400to 700 ng/dl sufficient for treating hypogonadism, according to the guidelines of the American Urology Association. Different studies comparing CC with testosterone gel concluded the same. Taylor and Levine (2010) (n = 103), demonstrated no difference in biochemical outcome of serum TT between CC or usage of testosterone gel.

Ramasamy et al. (2014) (n = 124) supported this finding between the effect of CC and testosterone gel but found a higher increase of serum TT in patients who used testosterone injections compared to CC or testosterone gel [15]. They found no difference in outcomes on the ADAM questionnaire between Testosterone treatment or CC therapy [15]. However, there are several advantages of CC over Testosterone treatment to mention. It is less expensive, noninvasive and fertility sparing. Furthermore, testosterone injections cause a high-peak increase of exogenous TT with potential higher risk of more side effects [15].

It has yet to be established what the most effective dosage of CC therapy is and by which patient characteristics this may be influenced. In the included studies, the dosage of CC varied between 25 and 50 mg/day and 25, 50, or 100 mg every other day according to Keihani et al. (2020) based the dosage of CC on bioavailable testosterone, BMI, patient preferences, and symptom severity [15]. However, there is lack of evidence for relevance of these variables. Four included studies titrated the dosage of CC based on TT level, measured after some time [15]. The best treatment strategy for this moment is to start with the lowest dosage, 25 mg every other day and titrating the dosage based on reached serum TT concentration and or symptom improvement [15].

Besides the biochemical response, the clinical response is equally important in the definition of hypogonadism [15]. Nevertheless, most included articles did not clearly describe and reported symptoms of hypogonadism as most important finding, next to the biochemical response. Krzastek et al. (2019) (n = 400), reported in >75% of the patients subjective hypogonadal symptom improvement (Follow up > 3 years) [15]. The ADAM questionnaire (with relatively high sensitivity but low specificity) is one of the most used and validated screening instruments.

In our review the ADAM score improved. However, 10% of the patients did not experience symptom improvement [27]. These results on the symptoms of hypogonadism should be interpreted with caution.

A placebo-controlled RCT (*n* = 17) from 1995 reported that the population could not discriminate for symptom improvement when they used CC and when they were on placebo [28]. Another study included RCT with placebo found a comparable improvement in both the CC group and placebo groups [29]. This could be explained by the lack of gradation in the severity of symptoms. However, when this RCT discriminated between items, they found an improvement in the CC group in ''erection strength'' and an improvement in ''libido'' in both groups. These contradictory effects of CC on symptoms of hypogonadism bring us to the conclusion that symptoms of hypogonadism are of multifactorial origin and complex to summarize in one questionnaire. Therefore, we advocate for the development and the implementation of a new or updated questionnaire for hypogonadism. One study as discussed above showed decrement of the libido using CC.

Elevated hematocrit, potentially leading to thrombo-embolic events, is one of the most concerning side effects for using CC. However, in the included studies, only one patient was described with elevated hematocrit [15]. An earlier study with 200 patients on CC showed that prevalence of polycythemia was lower in CC therapy than Testosterone therapy and did not develop a hematocrit high enough to require phlebotomy [20]. Studies have also shown that injectable testosterone poses a higher risk of iatrogenic polycythemia as compared to other modalities of treatment of male Studies have also shown that injectable testosterone poses a higher risk of iatrogenic polycythemia as compared to other modalities for treatment of male hypogonadism [30].

The CC treatment in majority of studies did not affect PSA, Lipid panel, Plasma glucose, prolactin levels and had much lesser incidence of being related to DVT compare to Testosterone treatment.

6. Conclusion

Clomiphene citrate for men with secondary/tertiary hypogonadism and structurally intact HT/HP axis, but physiologically changed improves both clinical symptoms and the biochemical testosterone insufficiency. Clomiphene citrate therapy has few reported side effects and good safety profile. It is probably necessary to stay on clomiphene citrate therapy to keep the biochemical and clinical effects. In our opinion, clomiphene citrate is a potential effective and safe treatment and should be considered as a therapy in men with symptomatic hypogonadism secondary/tertiary hypogonadism with structurally intact HT/HP axis especially for those with an active or future child wish.

Compliance with ethical standards

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