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Treatment of male hypogonadism with clomiphene citrate- where do we stay?

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Abstract

Clomiphene citrate (CC) was developed in 1956 as a selective estrogen receptor modulator and was subsequently used in clinical medicine starting in 1967, to treat female infertility. CC has also been used off-label to treat male infertility and hypogonadal symptoms. In this brief review, we will examine and summarize the available literature on CC and assess its efficacy in the treatment of male hypogonadism.

We performed an extensive review of the literature using the PubMed search engine. Our goal was to compare the FDA-approved treatment for male hypogonadism, testosterone, with CC treatment for male hypogonadism. We accessed and reviewed 29 relevant research articles. Our review revealed that CC increased serum testosterone levels, similar to the serum testosterone levels observed following testosterone gel application. We also found support for our contention that CC improves hypogonadal symptoms. An important difference between CC and testosterone is that CC appeared to preserve sperm production and maintain fertility. This is an important feature of CC treatment, as fertility is frequently desired in patients with secondary/tertiary hypogonadism. We also compared the safety of CC to testosterone and found that CC had a similar safety profile. In summary, CC appeared to be a suitable therapy for patients with male factor infertility and associated hypogonadal symptoms. However, based on our review, we found that more research is required to further examine CC's effectiveness for the treatment of these conditions.

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

1. Introduction

Hypogonadism is common, particularly in older men, with a prevalence rate of approximately 36% reported among men over age 45 who were not receiving testosterone supplementation [4]. Prevalence was also found to be exacerbated in men with a range of co-morbid conditions such as hypertension, type 2 diabetes, obesity, or prostate disease [4]. However, prevalence rates have also been reported to be substantially lower, with symptomatic hypogonadism in men between 40–79 years of age ranging from 2.1% to 13% [4]. According to the European Society of Urology guidelines (5), hypogonadism is of testicular origin (primary), hypothalamic-pituitary origin (secondary), mixed origin, or target-defect related [5]. Irrespective of etiology, low testosterone is frequently linked to a wide range of signs and symptoms depending on when the hypogonadism started, such as delayed puberty, small gonads, gynecomastia, infertility, low lean body weight, reduced strength, and several others [5]. Treatment of low T is typically not associated with an increased risk of prostate cancer progression or cardiovascular risk [2]. Common symptoms of hypogonadism are erectile dysfunction, reduced sexual activity and desire, loss of body hair, and decreased morning erections, among others. [4]. Other diseases, such as obesity, cardiovascular disease, chronic obstructive pulmonary disease (COPD), type 2 diabetes, HIV, chronic kidney diseases, malignancies, obstructive sleep apnea, cirrhosis of the liver, pituitary tumors,

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hyperprolactinemia, and several medications increase the risk of male hypogonadism. Finally, low testosterone level is frequently a sign of poor general health [6, 7].

The most frequent cause of hypogonadism appears to be primary hypogonadism. The diagnosis for primary hypogonadism is made with a determination of low serum testosterone concentration and high serum FSH and or LH concentration. The most common causes of primary hypogonadism are Klinefelter syndrome, chemotherapy, mumps, radiation therapy to the testes, and testicular tumors [6] Hyperprolactinemia, Kallmann's syndrome, obstructive sleep apnea, hemochromatosis, and select medications are more often associated with secondary and tertiary hypogonadism [7].

To the contrary, in secondary/tertiary hypogonadism the testes are intact but are not adequately stimulated by FSH or LH, which results in hypogonadism, typically with abnormally elevated FSH and LH. Secondary/tertiary hypogonadism is most often linked to hyperprolactinemia, Kallmann's syndrome, obesity, obstructive sleep apnea, medications, and hemochromatosis, among others [6]. Symptoms of testosterone deficiency that develop in men greater than age 40 are termed adult-onset hypogonadism in aging men (ADAM). In these cases, the HPG-axis function is normal [6, 7].

Men with hypogonadism are usually treated with testosterone replacement, the goal of which aims to increase serum testosterone. Restoration of serum testosterone can increase muscle mass, and physical strength, restore libido, increase bone density and improve overall well-being. However, testosterone therapy has notable side effects. The most common side effect in older men is polycythemia and in younger men, acne is common [8]. Testosterone therapy decreases fertility and if the male patient desires such therapy should not be prescribed [1].

Medications used for secondary/tertiary hypogonadism are human chorionic gonadotropin (hCG), Follicle stimulating hormone, and selective estrogen/androgen receptor modulators (SERMS and SARMS) [9]. The mechanism of action for CC is binding to hypothalamic and pituitary gland estrogen receptors which stimulate prolactin release and lead to the release of gonadotropins. Gonadotropins stimulate the testicles and increase testosterone production. CC has been used since 1960 to stimulate ovulation in women; however, recent uses in male patients have been off-label. CC is not yet approved for the treatment of hypogonadism in males because its effectiveness has not been established. However, CC is widely used in the medical practice for men with hypogonadism who want to preserve their fertility [1,10,11,12,13,14,15,16,17,18,19,20].

2. Mechanism of Action of Clomiphene Citrate

CC exerts its action in the hypothalamus as a competitive estrogen receptor modulator. CC competes with estradiol at the hypothalamic and hypophyseal receptor level and it increases GnRH release from the hypothalamus which stimulates LH and FSH release from the anterior pituitary. LH and FSH increase testicular testosterone and sperm production. The two components of CC are zuclomiphene (cis-isomer) and enclomiphene (68%). Unlike testosterone, these drugs do not suppress the HPG axis, but rather lead to an increase in LH and FSH [1, 16].

3. Adverse effects

CC is considered safe and is an inexpensive treatment for male hypogonadism [21]. The most commonly reported side effects are fatigue, breast tenderness, headache, flushing, and abdominal /pelvic pain. These side effects were found in 4-11% of male patients [6]. Wheeler et al. [22] reported a lower incidence of secondary polycythemia (1.7%) with CC compared to testosterone treatment (11.2%). In another study, CC did not significantly increase cholesterol, PSA, or hemoglobin [19].

Two cases are available in the literature that involved switching from testosterone replacement therapy to CC in a patient with secondary polycythemia [23, 24]. It was reported that these patients did not exhibit polycythemia when switched to CC. One of the patients had both polycythemia and TIA but after being switched to CC, his HCT normalized and his TIA symptoms resolved [22]. Kavoussi et al. [25]. Treated male patients with hypogonadism with testosterone replacement (n=694) or with CC (n=486) for 22 months. These authors reported a somewhat lower incidence of deep-vein thrombosis in the CC group but DVT was low in both groups and there was no evidence of polycythemia in either group [25].

4. When Clomiphene Citrate is used and what is its effective dose?

Clomiphene citrate is typically used off-label for male patients who desire fertility in the United States and suffer from secondary hypogonadism with intact HT-HP axis. However, CC use for these patients is not FDA-approved, because of the inconsistency in the data [26, 27, 28] CC increases the total and free testosterone and also increases LH, FSH, and estradiol. The ratio of testosterone/estradiol typically increases in patients taking CC [29]. Thus, CC is effective for improving endogenous testosterone secretion by stimulating the HT-HPG-axis in male patients suffering from hypogonadism. CC has been shown to increase total testosterone as much as testosterone gel and achieves optimal male reference range, 400-700 ng/dl [10, 14, 17]. This is the optimal level of total testosterone which needs to be achieved in the treatment of male hypogonadism. Testosterone injections increase the total testosterone more than either testosterone gel or CC, but for all clinical purposes this is not needed [17]. There are some advantages of CC over testosterone treatment. It is less expensive, non-invasive and is especially useful in male patients who want to preserve their fertility.

The dose used in different clinical scenarios was between 25 mg of CC every other day to 100 mg a day [10]. We recommend a treatment strategy of starting the CC treatment with the lowest dose (25 mg) every other day and titrating based on clinical and biochemical responses.

Our review of the literature revealed that the ADAM score improved with CC treatment; however, 10% of the patients did not experience symptom improvement [30]. We believe these results should be interpreted with caution, because of the design of some of the studies and the lack of an appropriate questionnaire to grade the hypogonadal symptoms. We believe such a questionnaire needs to needs to be developed [31, 32].

The CC treatment in the majority of studies did not affect the patients' PSA, lipid panel, plasma glucose, prolactin levels and showed a much lower incidence of being related to DVT compared to Testosterone treatment [21].

5. Conclusion

Clomiphene citrate for men with hypogonadism and intact HT/HP/gonadal axis, improved both clinical symptoms and the serum testosterone levels. Fortunately, there are few reported side effects with the clomiphene citrate therapy as the drug has a favorable side effect profile. Lifelong treatment with clomiphene citrate is likely necessary for the clinical and biochemical effect to endure. We believe that clomiphene citrate is a potentially effective and safe treatment for men with symptomatic hypogonadism especially if fertility is desired and alternative to the officially acknowledged treatment by AUA with Testosterone].

Compliance with ethical standards

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References

[1] Bryan J Herzog, Hoang MinhTue Nguyen et al. Clomiphene citrate for male hypogonadism and infertility: An Updated Review. Andogens: Clinical Research and therapeutics, Vol1, No 1, 9 Oct 2020: https://doi.org/10.1089/andro.2020.005

[2] Wiehle R, Cunningham GR, Pitteloud N, et al. Testosterone restoration using enclomiphene citrate in men with secondary hypogonadism: a pharmacodynamic and pharmacokinetic study. BJU Int. 2013; 112: 1188– 1200.

[3] Taylor F, Levine L. Clomiphene citrate and testosterone gel replacement therapy for male hypogonadism: efficacy and treatment cost. J Sex Med. 2010; 7: 269– 276. PMID: 1969492

[4] Mulligan, T., Frick, MF, Zuraw, QC, Stemhagen, A, McWhirter, C. Prevalence of hypogonadism in males aged at least 45 years: the HIM study. International Journal of Clinical Practice, 60(7), 762-769. 2006. https://doi.org/10.1111/j.1742-1241.2006.00992.

[5] Dohle, GR. Arver, S, Bettocchi, TH, Kliesch, S, Punab, M. EAU Guidelines on male hypogonadism. European Association of Urology, 2016 https://www.nebido.com/sites/g/files/vrxlpx5371/files/2020-10/EAU-Guidelines-Male-Hypogonadism-2016.pdf Accessed: 8/19/2022.

[6] Manou Huijben 1, M Tycho W T Lock 1, Vincent F de Kemp 1, Laetitia M O de Kort 1, H M K van Breda . Clomiphene citrate for men with hypogonadism: a systematic review and meta-analysis. Andrology.2022 Mar;10(3):451-469: Doi: 10.1111/andr.13146.Epub 2022 Jan 8. PMID: 34933414

[7] Hall SA, Esche GR, Araujo AB, et al. Correlates of low testosterone and symptomatic androgen deficiency in a population-based sample. J Clin Endocrinol Metab. 2008: 93: 3870– 3877. PMID: 18664536

[8] Pastuszak AW, Gomez LP, Scovell JM, Khera M, Lamb DJ, Lipshultz LI. Comparison of the effects of testosterone gels, injections, and pellets on serum hormones, erythrocytosis, lipids, and prostate-specific antigen. Sex Med. 2015; 3(3): 165– 173. PMID: 26468380

[9] Crosnoe-Shipley LE. Treatment of hypogonadotropic male hypogonadism: case-based scenarios. World J Nephrol. 2015; 4(2): 245– 253. PMID: 25949938

[10] Da Ros CT, Averbeck MA. Twenty-five milligrams of clomiphene citrate presents positive effect on treatment of male testosterone deficiency - a prospective study. Int Braz J Urol. 2012;38:512–518. PMID: 22951175

[11] Taylor F, Levine L. Clomiphene citrate and testosterone gel replacement therapy for male hypogonadism: efficacy and treatment cost. J Sex Med. 2010;7:269–276 PMID: 19694928

[12] Moskovic DJ, Katz DJ, Akhavan A, Park K, Mulhall JP. Clomiphene citrate is safe and effective for long-term management of hypogonadism. BJU Int. 2012; 110(10): 1524– 1528. PMID: 22458540

[13] Katz DJ, Nabulsi O, Tal R, Mulhall JP. Outcomes of clomiphene citrate treatment in young hypogonadal men. BJU Int. 2012;110:573–578 PMID: 22044663

[14] Kaminetsky J, Werner M, Fontenot G, Wiehle RD. Oral enclomiphene citrate stimulates the endogenous production of testosterone and sperm counts in men with low testosterone: comparison with testosterone gel. J Sex Med. 2013;10:1628–1635. PMID: 23530575

[15] Dadhich P, Ramasamy R, Scovell J, Wilken N, Lipshultz L. Testosterone versus clomiphene citrate in managing symptoms of hypogonadism in men. Indian J Urol. 2017; 33(3): 236. PMID: 28717276

[16] Wheeler KM, Sharma D, Kavoussi PK, Smith RP, Costabile R. Clomiphene citrate for the treatment of hypogonadism. Sex Med Rev. 2019; 7(2): 272– 276. PMID: 30522888

[17] Ramasamy R, Scovell JM, Kovac JR, Lipshultz LI. Testosterone supplementation versus clomiphene citrate for hypogonadism: an age matched comparison of satisfaction and efficacy. J Urol. 2014; 192(3): 875– 879. PMID: 24657837

[18] Delu A, Kiltz RJ, Kuznetsov VA, Trussell TL. Clomiphene citrate improved testosterone and sperm concentration in hypogonadal males. Syst Biol Reprod Med. 2020; 66(6): 364– 369. PMID: 33043679

[19] Taylor F, Levine L. Clomiphene citrate and testosterone gel replacement therapy for male hypogonadism: efficacy and treatment cost. J Sex Med. 2010; 7: 269– 276. PMID: 19694928

[20] Liel Y. Clomiphene citrate in the treatment of idiopathic or functional hypogonadotropic hypogonadism in men: a case series and review of the literature. Endocr Pract. 2017; 23(3): 279– 287. PMID: 27849376

[21] Patel DP, Brant WO, Myers JB, et al. The safety and efficacy of clomiphene citrate in hypoandrogenic and subfertile men. Int J Impot Res. 2015; 27(6): 221– 224. PMID: 26289907

[22] Wheeler KM, Smith RP, Kumar RA, Setia S, Costabile RA, Kavoussi PK. A comparison of secondary polycythemia in hypogonadal men treated with clomiphene citrate versus testosterone replacement: a multi-institutional study. J Urol. 2017. 197(4): 1127– 1131. PMID: 27984109

[23] Cangiano B, Cacciatore C, Persani L, Bonomi M. Switch to restoration therapy in a testosterone treated central hypogonadism with erythrocytosis. Endocrinol Diabetes Metab Case reports; 2017 Jul 7; 2017:17-055; PMID: 28721216: doi: 10.1530/EDM-17-0055.

[24] A. Manov, A. Hatharasinghe et al. Effective Treatment of Secondary Hypogonadism with Clomiphene Citrate in a Male Patient with Secondary Polycythemia and History of Transient Ischemic Attack. J Endocrinol 2020, 4(2): 000153 . DOI:10.23880/OAJE-16000153.

[25] Kavoussi, PZ, Machen, GL, Wenzel, JL, Ellis, AM, Kavoussi, M, Kavoussi, KM, Kavoussi, SK. Medical Treatments for Hypogonadism do not Significantly Increase the Risk of Deep Vein Thrombosis Over General Population Risk. Urology, 124: 127-130, 2019.

[26] Lindsey E Crosnoe-Shipley et al. Treatment of hypogonadotropic male hypogonadism: Case -based scenarios; World Journal Nephrol,2015 May 6;4(2):245-253.Doi:10.5527/wjn.v4.i2.245; pubmedid:25949938

[27] Bhasin S, Brito JP, Cunningham GR, Hayes FJ, HodisHN, et al. (2018) Testosterone Therapy in Men With Hypogonadism: An Endocrine Society Clinical Practice Guideline. The Journal pf clinical endocrinology and metabolism 103(5):1715-1744

[28] Lo Eric M, Rodriguez KM, Pastuszak AW, Khera M (2018) Alternatives to testosterone therapy: Review. Sex med Rev 6(1):106-113

[29] Shabsigh A, Kang Y, Shabsign R, et al. Clomiphene citrate effects on testosterone/estrogen ratio in male hypogonadism. J Sex Med. 2005; 2(5): 716– 721 PMID: 16422830

[30] Katz DJ, Nabulsi O, Tal R, Mulhall JP. Outcomes of clomiphene citrate treatment in young hypogonadal men. BJU Int. 2012; 110(4): 573– 578 PMID: 22044663

[31] Guay A, Heatley GJ. Effect of raising endogenous testosterone impotent. J Clin Endocrinol Metab. 1995; 80(12): 3546– 3552 PMID: 8530597

[32] Soares AH, Horie NC, Chiang LAP, et al. Effects of clomiphene citrate on male obesity-associated hypogonadism: a randomized, double-blind, placebo-controlled study. Int J Obes. 2018; 42(5): 953– 963.

[33] Mulhall, John P., et al. Evaluation and management of testosterone deficiency: AUA guideline." The Journal of urology 200.2 (2018): 423-432.