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Commentary about treatment of male hypogonadism with clomiphene citrate compare to treatment with testosterone

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Abstract

Clomiphene citrate (CC) is a selective estrogen receptor modulator and estrogen antagonist. It was introduced into clinical medicine in 1967 for the treatment of female infertility. CC has also been explored for off-label use for male infertility and male hypogonadal symptoms. We want to comment and discuss medical literature on CC and its contribution to the treatment of male hypogonadism. The main goal of the commentary is to discuss mechanism of action of CC and when it can be used for treatment of male hypogonadism instead of Testosterone which treatment is FDA approved. [1,2]. CC increases the Testosterone level in the blood similar to Testosterone gel. It improves the hypogonadal symptoms as well. The difference with CC and Testosterone is that CC preserves the sperm production and fertility if fertility is desired in patients with secondary/tertiary hypogonadism. The safety of CC was compared to Testosterone safety as well. 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.

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

1. Introduction

Hypogonadism is a common medical condition among men. We subdivide it to Primary from testicular origin and secondary from Hypothalamic-pituitary origin, mixed origin or target -defect related. Low testosterone is frequently linked to wide range of signs and symptoms, which depends when in the male development it occur, such as delayed puberty, small gonads, gynecomastia, infertility, low lean body weight, reduced strength and several others. Treatment of low T is typically not associated with increased risk of prostate cancer progression or cardiovascular risk. Common symptoms of hypogonadism are erectile dysfunction, reduced sexual activity and desire, decreased morning erections among others. The symptomatic hypogonadism occurs between the age of 40–79 years in 2.1% to 13% of men and increases with age [1]. Other diseases increase the risk of male hypogonadism like 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 and also, many medications among others. Low testosterone level is frequently a sign of poor general health [2,3].

Primary hypogonadism is the most frequent cause of hypogonadism, The diagnosis is made by finding low serum testosterone concentration and high serum FSH and or LH concentration. The most common reasons are Klinefelter syndrome Chemotherapy, mumps, Radiation therapy to the testes and testicular tumors [2]. Hyperprolactinemia,

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Kallmann's syndrome, Obstructive sleep apnea, hemochromatosis, medications or multiple congenital disorders are associated with secondary and tertiary hypogonadism [3].

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 [2]. Symptoms of testosterone deficiency that develop in men greater than 40 is termed Adult-onset hypogonadism in Aging men (ADAM). The HPG-axis function is normal [2,3].

FDA approved treatment in USA for male hypogonadism is with testosterone replacement therapy. Achieving normalserum can increase the muscle mass, physical strength, restore libido, increase bone density and improve overall well-being. TTh has some notable side effects. The most common side effect in older men is polycythemia and in younger acne [4]. Testosterone therapy decreases fertility and if the male patient desires such should not be prescribed.

Medications used for secondary/tertiary hypogonadism are human chorionic gonadotropin (hCG) plus minus FSH injections and selective estrogen/androgen receptor modulators (SERMS and SARMS) [5].

Clomiphene citrate (CC) is a SERM occupying estrogen receptors in the hypothalamus and pituitary leading to gonadotropin release, which leads to increased testicular stimulation and testosterone production. CC is used from 1967 for female infertility and it has been used off-label for men [11,12,14,16,17].

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

1.1. Mechanism of Action of Clomiphene Citrate

CC is competitive estrogen receptor modulator in the hypothalamus. It competes with estradiol at the hypothalamic and hypophyseal receptor level. It increases GNRH from the hypothalamus which increases the LH and FSH from the anterior hypophyseal gland. LH and FSH increase the testosterone and sperm production from the testes. The two components of CC zuclomiphene (cis-isomer) and 62% enclomiphene unlike testosterone, both do not suppress the HPG axis, but actually lead to an increase in LH and FSH [6,7,8,9,10].

1.2. Adverse effects

CC is considered safe and not expensive treatment for male hypogonadism [19]. Most commonly reported side effects are fatigue, breast tenderness, headache, flushing, abdominal /pelvic pain. These side effects were found in 4-11% of male patients [2].

Wheeler et al. reported lower incidence of secondary polycythemia with CC compare to Testosterone treatment -1.7% compare to 11.2 % [18].

CC did not significantly increase cholesterol, PSA, or hemoglobin in another study [15].

Two cases are available in the literature with switching TRT to CC in a patient with secondary polycythemia on TRT. These patients did not exhibit polycythemia on CC. One of the patients while receiving Testosterone therapy had polycythemia and TIA's, but after the switch from Testosterone to CC his HCT normalized and he did not have any more TIA symptoms [19,20].

Kavoussi et al. treated male patients with Hypogonadism with testosterone replacement (n=694) and with CC (n=486). The treatment duration was 22- months [12].

Discussion

Clomiphene citrate is used off label in USA in male patients who suffer from secondary hypogonadism with intact HT-HP axis which might have some physiological change who desire fertility although not FDA approved, because of inconsistency of the data [21,22,23].

The drug increases the total and free Testosterone (TT), the LH, FSH, and estradiol also increases. The ratio Testosterone/estradiol increases [24]. The increased serum levels of testosterone and gonadotrophins show that CC is effective in improving endogenous testosterone secretion by stimulating the HT-HP-G-axis in male patients suffering

from hypogonadism. CC increases the TT as much as testosterone gel and achieves serum value in optimal male reference range of 400-700 ng/dl. This is the optimal level of total testosterone which needs to be achieved in treatment of male hypogonadism. Testosterone injections increase the total testosterone more than testosterone gel or CC , but for all clinical purposes this is not needed [13].

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. We can recommend treatment strategy of starting the treatment with cc with the lowest dose of 25 mg every other day and titrate based on response- clinical and biochemical.

In our review of the literature the ADAM score improved. However, 10% of the patients did not experience symptom improvement [25]. These results of symptoms of hypogonadism should be interpreted with caution, because of the design of some of the studies and lack of appropriate questionnaire to grade the hypogonadal symptoms which needs to be developed [26,27].

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.

2. Conclusion

Clomiphene citrate for men with hypogonadism and intact HT/HP/gonadal axis, but physiologically changed improves both clinical symptoms and the serum testosterone levels Fortunately, there are few reported side effects with the Clomiphene citrate therapy. Additionally, the drug enjoys a favorable side effect profile. Lifelong treatment with clomiphene citrate is likely necessary for the clinical and biochemical effect to endur. Clomiphene citrate is a potential effective and safe treatment in men with symptomatic hypogonadism especially if fertility is desired.

Compliance with ethical standards

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