The Use of Comiphene Citrate in Young Adults With Low Testosterone and Symptoms of Hypogonadism

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ABSTRACT

Background: Clomiphene Citrate (CC) is a selective estrogen receptor modulator that has been used in women to induce ovulation for years. Recently Clomiphene Citrate has bee used as an off label treatment in men with hipogonadism. CC acts centrally inducing production of Testosterone and improving spermatogenesis.

Methods: From March 2016 to January 2019, 46 patients were observed. They received a prescri ption of CC, 50 mg/daily, during 6 months. All patients had Total Testosterone levels less than 300 mg/dl, associated to sign and symptons of Hipogonadism (HG).

Results: After 180 days of CC prescription, 34 (73,91%) patients from 46, had raised levels of Total Testosterone.

Conclusions: Clomiphene Citrate (CC) is an effective oral medication to improve Testosterone production.

INFORMAÇÕES

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Palavras-Chave:
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INTRODUCTION

Clomiphene citrate (CC) is drug used frequently in ovarian stimulation procedure. However, it has been used as "off label" therapy in men, to achieve testicular stimulation to increase testosterone levels, as an alternative way, from use of testosterone replacement therapy (TRT).

OBJECTIVE

Evaluate the effectiveness and safety of Clomiphene citrate (CC) in adult young men in reversing the signs and symptoms related to hypogonadism (HG) with raising of testosterone levels.

MATERIAL

In a prospective study, single-arm, 46 patients were followed, from March 2016 to January 2019. The age ranging from 27 to 42 years. The inclusion criteria was clinical and laboratory finding of hypogonadism. Were included in the group patients with symptoms of: a lack of libido, erectile dysfunction, physical and mental performance decline, worsening of mood. All patients presented total testosterone level less or equal to 300 ng/dl, collected in the morning, until the 9:00 am. The prolactin and estradiol levels should be normal in all patients of this group. One sperm sample was collected from all patients, before start the study and after 180 days. The sperm should be normal (concentration number, morphology and motility) to be part of this stydy. The patients were told

about benefits and risks of testosterone replacement therapy (TRT) with gel or injection and about therapy to induce testosterone production (TITP). All patients signed the term informed consent prior to inclusion in the study. The patients received 50 mg Clomiphene citrate daily, single dose, for 180 consecutive days. The dosage of total testosterone was held in 30, 90 and180 days after study began.

RESULTS

From total of 46 patients who initiated the study, 12 were excluded because stopped the use of CC. Twenty two (47,82%) patients had increased levels of testosterone at the first 30 days with improvement of symptoms. Thirty two patients, (69,56%) showed increased levels of testosterone to 90 days of treatment, with improvement of symptoms. And 34 patients (73,91%) showed normal levels of TT at the end of 180 days. During the stydy, 12 (26,08%) patients were excluded. No one patient from this group, 34 patients, showed decrease of sperm parameters after 180 days.

DISCUSSION

The Hypogonadism (HG) is associated to decrease of testosterone levels. testosterone is responsible to male sexual characters and regulates libido, sexual performance, fertility, muscle mass, red blood cell production, mood, and fat distribution.[1,3,5,8,9,10,12] The HG can be classified as primary, when pituitary gland production of FSH and LH is low. The secondary hypogonadism occurs when the testes do not produce the T, independent of the central stimulus. In this situation, FSH and LH levels are finding up from normal range. It is known that physiologically, men at 40 years, tend to decrease the production of testosterone in about 1% per year.[1,3,5,8,9,10,12,17] From this age group, the studies in literature estimates that between 5 to 10% of the male population suffer low testosterone symptoms.[1,3,5,8,9,11,12]

The diagnosis of HG is based on clinical complaint: lack of libido, worsening sexual performance, emotional lability, fall of physical and mental performance,

accumulation of abdominal fat, osteoporosis, etc.[8,9,10,11,14] The laboratory diagnosis is confirmed by the total testosterone level equal or below 300 ng/dl, according to the guidelines from many urologics associations as AUA and BSU.[8,9,12] The goal of treatment of HG is focused on increasing the levels of testosterone and restore mainly sexual performance. Currently we use the injectable formulations of testosterone: Undecanoate of testosterone, Cipionate of testosterone or in gel forms (testosterone gel between 20 to 50 mg.) [1,3,9,10,11,12] Each one of that with diferences at composition, in a half – time life, and diferent costs. The patients preferences may vary from one than another, most of time without cientific explanation.[1,3,8,9,10,11,12]

The Testosterone Replacement Therapy will fast increase levels of testosterone in a bloodstream. The testosterone will easily cross the wall cell to linkeage inside the citoplasm to testosterone receptor, now as DHT (dihidrotestosterone) to realize the expected metabolics and anabolics effects.[1,2,3,7,8,9,12]

However in common mechanism by use of any kind of TRT, is in supress of the hipothalamic-pituitary – gonadal axis.[1,8,9,10,17] The raising levels of TT in the bloodstream, blocks by positive feedback; the release of GnRH from the hypothalamus and consequently the release of FSH and LH, from the pituitary gland.[8,9,12,14,17,18]

Leading the supression of natural production of testosterone, and the supression of spermatogenesis process too. (17,18) It is not uncommon to

find men in TRT with decreased testicular function and orgam size.[15,16,17,18] In another hand, Clomiphene citrate (CC), is well known antagonistic to the estrogens receptors in women.[6] It is well established that he competes with the natural estrogen receptors in the hypothalamus, causing increased level of GnRH (gonadotropin releasing hormone) and consequent increase in FSH and LH. Is commonly used at human reproductive laboratories in order to stimulate ovulation, to natural conception or artificial insemination procedure.[6]

In young men, CC has been used as “off label” practice to induce testosterone production.[1,2,11,12,14]

With similar biochemical effect, CC cause increasing levels of FSH and LH, stimulating the testes to produce more testosterone and more sperm.[12,14,15,16,17,18]. Some studies have reported the improvement in bone density, mood, memory, well being and loses of abdominal fat, all of that associated to increase of testosterone.[7,8,9,10,12,13]

In the current study, we did not find decrease in spermatogenesis. In literature is described some adverse effects of CC including: gynecomastia, headache and psychiatric illnesses[12,13,14] CC is generally considered to be safe and well tolerated medication.[13,14,15,16,17,18]

In the patients who participated in this study, the improvement of symptoms were directly associated to increased levels of total testosterone. In the first serum sample collected with 30 days, 22 patients (47,82%) already had improvement of symptoms and signs of HG. However throughout the study, 12 patients (38,33%)withdrew from the study due to various causes: cost of the medication, side effects, lack of effectiveness of medication. One important report was that in patients that justified the stop from use the medication, 4 patients, showed increased levels of T, but they had not seen the improvement of symptoms of hypogonadism.

CONCLUSION

The improvement of total testosterone levels and increase of symptoms and signs of hypogonadism is a feasible. The use of CC is effective and safe alternative to patient that want to preserve fertility and need to increase testosterone levels. More studies should be done to observe the results of long period of CC use.

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