Clomiphene Citrate in Obesity - Associated Hypogonadism

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Abstract: This study investigates the benefits of Clomiphene Citrate CC in treating obesity-associated secondary hypogonadism. An integrative review was conducted, focusing on pharmacodynamic principles, risk-benefit, safety, and therapeutic effectiveness. The study concludes that CC is a safe and effective therapy for hypogonadotropic hypogonadism, especially beneficial for those desiring fatherhood.

Keywords: Hypogonadism. Male Obesity, ClomiphenCitrat. Fertility, Hypothalamic-Pituitary-Gonadal Axis

1. Introduction

The World Health Organization (WHO) defines obesity as a chronic disease, associated with abnormal or excessive accumulation of fat in the body, and its origin is associated with multifactorial causes, such as biological, social, cultural and behavioral. It is estimated that a total of 2 billion people are overweight and of these, 650 million are obese and subject to conditions associated with this comorbidity [1].

In obesity, the adipose tissue is metabolically active and, mainly, that of visceral origin has a deleterious potential with the secretion of pro-inflammatory adipokines, resulting in insulin resistance, a low-grade chronic inflammatory and procoagulant profile [2]. Among the risk factors, it is evident that it is one of the main causes of secondary hypogonadism in men, due to the impairment of the hypothalamic-pituitarygonad axis (HHG), in which the signs and symptoms will be better detailed below [3].

Given the above and to better elucidate its mechanism and the steroidogenesis responsible for the formation of testosterone, it is necessary to understand the gonadal axis. In a simplified way, we can divide the pathway into three levels: hypothalamus, pituitary and gonads. In the hypothalamus we have the synthesis and pulsatile release of gonadotropin-releasing hormone (GnRH), which in turn stimulates the pituitary to produce gonadotropins, namely Luteinizing Hormone (LH) and Follicle-stimulating Hormone (FSH), which respectively stimulate the Leydig cells to produce testosterone and Sertoli cells to carry out spermatogenesis. If the axis is inhibited at any of the levels, we have hypogonadism [3]. Hypogonadism, in turn, is a clinical syndrome characterized by the presence of serum levels of total testosterone (TT) below 300ng/dL, associated with signs and symptoms of low testosterone levels, resulting from a dysfunction of the HHG axis, based on in the guideline of the American Urological Association (AUA) [4].

The clinical picture can range from asymptomatic forms to body and sexual changes, resulting in a nonspecific picture such as weakness, fatigue, depression and changes in body composition by favoring, mainly, adipogenesis. Among sexual symptoms, we have reduced libido, erection and increased erectile dysfunction. In addition, there is damage to bone mineral density and muscle formation [5].

Among its classifications, it is possible to associate obesity with subtypes of hypogonadism, with emphasis on functional or secondary hypogonadism, of central origin with alteration at the hypothalamic or pituitary level, with consequent reduction in the production of gonadotropins (LH and FSH), through estrogenic counter-regulation with the HHG axis in obese patients, as will be described below. It can also be called hypogonadotrophic hypogonadism, due to the presence of hypofunctioning glands [1].

For endocrine-metabolic replacement, the scientific community has several therapeutic alternatives, among which Testosterone Replacement Therapy (TRT) stands out. This, with the action of its active metabolites, acts on several systems through its androgenic effects, such as improving bone mineral density, erectile function and body composition. Its pharmacodynamics predicts the reduction of adipose tissue, which results in lower peripheral

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conversion of estradiol through the aromatase enzyme, present mainly in adipocytes. However, among its adverse effects, the reduction of fertility with a decrease in testicular volume and alteration of spermatogenesis, mainly in the long term, stands out. In addition, there are also deleterious alterations in several systems such as the cardiovascular, renal, hepatic and neurological and metabolic alterations when this therapy is used in supraphysiological doses [6].

In this sense, as another therapeutic resource, there is the use of Clomiphene Citrate (CC), intended for patients who, in addition to the treatment of hypogonadism, express the desire for fatherhood. Thus, it becomes evident that the main benefit of selective estrogen receptor modulators (SERM) is not to induce the adverse effects obtained with the use of testosterone replacement therapy, such as testicular atrophy or suppression of spermatogenesis, these being fundamental points for maintenance of male fertility [6].

Among the SERMs, the CC stands out, whose mechanism of action is to bind to specific estrogen receptors in the hypothalamus, without stimulating them, which prevents the negative feedback that endogenous estrogen presents when binding to these receptors. With this, we will have the reestablishment and maintenance of the HHG axis, with the pulsatile release of gonadotropin-releasing hormone (GnRH) and consequent production of pituitary gonadotropins, which would improve spermatogenesis and, consequently, fertility, with the recovery of previously atrophied testicular volume [6,7].

In this context, this investigation is justified, as it seeks to elucidate the beneficial effect of CC when applied to obese patients with hypogonadotropic hypogonadism who desire fertility.

2. Material and Methods

This is an integrative review, with a study based on a compilation of evidence in the literature that is based on a primary study that justifies the objective of the research. Thus, a comprehensive literature search was carried out, in an impartial and reproducible manner, with the aim of evaluating and synthesizing the set of evidence from scientific studies.

For data collection, a structured instrument (synoptic table) was developed, consisting of five items to assist in the recording and analysis of information, which were divided by title, author, year of publication, journal name and general research objective (table 1) [8].

The research design was carried out in a clear and objective way and its structure agreed through well-defined steps, which were carried out through a hierarchy process, as explained below.

Step 1: Definition of eligibility criteria

The eligibility and inclusion criteria for the survey were defined using the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) strategy. This methodology performs screening and systematically identifies reports that fit the review [9]. Among the eligibility criteria, articles were chosen that included Clomiphene Citrate as a therapeutic approach for hypogonadism, prioritizing the most recent ones in different languages.

Step 2: Formulation of the research question and definition of descriptors

At this stage, the use of the PICO acromion was fundamental, with the purpose of directing research questions and improving scientific evidence. In this, we have: P (population), I (intervention), C (control) and O (Outcome-Outcome) [10].

Step 3: Search the database

The main databases searched were: MEDLINE, which includes the Medical Literature Analysis and Retrieval System Online and PubMed; EMBASE, which includes Elsevier and Scientific and Technical Literature of Latin America and the Caribbean (LILACS); and the Virtual Health Library (VHL). In addition to these, a manual search for sources of primary studies was also performed.

Step 4: Study selection strategy

The selection of studies was performed using the Rayyan platform, which in turn optimizes the initial screening of abstracts and titles for systematic review. For this, it has in its software a semi-automotion incorporated with its high degree of usability [11].

Step 5: Evaluation of primary studies

In this step, the quality and biases of each research were evaluated, in order to establish a standard in the quality of the evidence available in each study.

Step 6: Synthesis and conclusion through analysis of results

The synthesis and conclusion of the collected data were made through a quantitative analysis of the obtained results, which clearly elucidated and directed the research objectives.

3. Results

After searching the databases, 73 articles were located and incorporated into the Rayyan platform, and only articles from MEDLINE and PubMed that fit the scope of the research were selected. Of these, 51 articles were excluded due to duplicity and for not meeting the eligibility criteria. Therefore, 22 articles were selected for reading in full, with a final sample of 16 articles, described in figure 1.

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Figure 1: Study selection process flow diagram

4. Discussion

The result of the research was discussed, in which articles within the present were integrated with preference for articles within the period of 2020 and 2023. The study sought to elucidate, in view of the available literature, what are the therapeutic advantages in the treatment of hypogonadism in obese patients with desire for fatherhood.

Hypogonadism, as mentioned above, is a clinical condition marked by the inability of the testes to produce physiological levels of testosterone and an adequate number of spermatozoa, due to the failure of one or more items of the gonadal axis. It may be of congenital or acquired origin, the latter being induced by the pathophysiological mechanism through which obesity permeates [1].

Therefore, obesity-related hypogonadism is one of the main risk factors for the development of chronic diseases, with an impact on several systems, such as the cardiovascular, hepatic, and respiratory systems, in addition to interfering with the quality of sleep, for example. through the propensity for Obstructive Sleep Apnea and Hypopnea Syndrome (OSAHS). Several mechanisms may negatively affect the HHG axis, such as increased conversion of testosterone to estradiol by aromatase enzyme activity in adipose tissue, increased production of Reactive Oxygen Species (ROS) and release of various inflammatory cytokines by direct and indirect means. Thus, androgen deficiency can be accelerated by the expansion of adipose tissue, increasing obesity, which in turn increases hypogonadism, thus providing a vicious cycle. Thereby, it is necessary to introduce therapeutic measures in order to avoid such losses [3].

According to Ide, Vanderschueren, Antonio L. (2020) [5], in addition to lifestyle and behavioral changes, there are at least three ways to treat functional hypogonadism, namely testosterone replacement therapy, Human Chorionic Gonadotropin (hCG) and Clomiphene Citrate.

Exogenous testosterone, which is now considered the gold standard for this condition, has a mechanism of action that is similar to the effect produced physiologically. Thus, it has the ability to penetrate the cell membrane of the target cell and bind to an androgen receptor, thus forming a homodimer that moves to the cell nucleus and is responsible for positively regulating gene transcription and protein synthesis, being its systemic anabolic and androgenic repercussions [12, 13].

Regarding the androgenic effects of testosterone, we have those correlated with the reproductive tract, hair growth and sebaceous gland activity. With regard to anabolic effects, we have increased nitrogen fixation, collagen synthesis, muscle growth and aid in bone metabolism with improved bone mineral density (BMD) [5,12]. With regard to the metabolic fate of testosterone when systemically released, it can go through two metabolic pathways, one portion being converted into 17β-estradiol by means of the aromatase enzyme and the other into dihydrotestosterone (DHT) by means of the 5a-reductase enzyme. Such pathways will depend on individual factors, such as the body composition of each patient, since adipose tissue has a higher concentration of aromatase, leading to an increase in 17βestradiol, which is associated with unwanted effects such as gynecomastia, fluid retention, sexual dysfunction and risk of thromboembolism. On the other hand, DHT has a three times greater affinity for androgen receptors, exhibiting positive actions on sexual libido and erectile function, although it expresses some side effects, such as acne, alopecia and benign prostatic hyperplasia [12].

As a therapeutic alternative, we can make use of hCG considered a hormone homologous to LH that stimulates endogenous testosterone production through steroidogenesis in testicular tissues by Leydig cells [14]. Despite of this promising character, there is still little literature, and its effective use is mainly for patients with late-onset hypogonadism, so that its main indication is not fertility. The use of this monotherapy can promote a serum testosterone increase of more than 250 ng/dl, and its treatment is safe and effective, with no reports of complications or side effects in patients with hypogonadism [15]. It is applied subcutaneously and its half-life is relatively short, in addition to its high cost, which prevents it from being the first choice treatment, even in monotherapy or in combination [12, 16].

With regard to CC, as it is a selective modulator of estrogen receptors with central action (hypothalamus-pituitary), it acts by preventing the binding of circulating estrogen to estrogen receptors at the central level. Thus, there is a reduction in estrogenic counter regulation on the gonadal axis, which would culminate in a lower release of the hormones FSH and LH and, consequently, results in an improvement in serum testosterone levels and sperm count. Studies indicate that about 33% of men who used this medication daily previously had less than 5 million spermatozoa and, later, evolved to more than 5 million [17].

A study was carried out with a group of 400 men who had hypogonadism and used Clomiphene Citrate, of which 120 treated for more than 30 years and of these, 88% showed improvements in testosterone levels (reaching eugonadism) and 77% reported improvement symptoms caused by hypogonadism. With regard to the side effects caused by this

headache, visual blurring, mood therapy, swings, gynecomastia and increased breast sensitivity can be highlighted. In view of this, it can be stated that due to the range of benefits indicated with the use of CC, both in relation to serum testosterone levels and in the spermogram, this drug is a promising therapy for men of childbearing age with a desire for fatherhood [6, 18]. In view of the results described in Salter CA et. al (2019) [19], a successful treatment is equivalent to a minimum increment of 200ng/dl in total testosterone (TT) levels. Thus, through a retrospective cohort study, an analysis was carried out among 332 men aged between 31 and 40 years old, during a 6-month interval in the use of CC to evaluate the response and therapeutic effectiveness, demonstrating that 73 % of this sample had a minimum increase of 200ng/dL and an average increase of 329ng/dL in TT values. In addition to this analysis, the ADAM (Androgen Deficiency in Aging Males) form was used, which has been validated as a diagnostic tool for androgen disorders in male aging, based on symptoms of hypogonadism [20].

In addition to the aforementioned studies, in Wong SK et al. (2019) [21], beneficial effects were also evidenced in other systems affected by hypogonadism, such as the skeletal system. The study in question classified as a retrospective cohort sampled 46 patients who had serum testosterone levels below 228 ng/dL. The benefits of this analysis were based on the improvement in the relationship between osteopenia and osteoporosis, showing potential for improvement in bone microstructure and even bone strength in men.

In order to correlate the reestablishment of the gonadal axis and the therapy with CC, a meta-analysis was carried out on a compilation of 17 studies, among these, four randomized clinical trials with a higher degree of evidence and relevance in the scientific literature with a total sample of 1,279 participants. In this study, a good therapeutic response was elucidated with rates varying between 62 and 81%, with good efficacy for symptoms related to reduced levels of total testosterone, with emphasis on improvement in sexual parameters and without great evidence of improvement in lipid pattern and body composition. In addition, it has proven safety and reduced side effects. Another benefit that becomes evident is that after a certain period, it is possible to discontinue the medication with the maintenance of TT within the therapeutic target [22].

5. Conclusion

Finally, in view of the above, it is a fact that Clomiphene Citrate is an effective and safe therapy for hypogonadotropic hypogonadism, with benefits in endocrine-metabolic factors, in addition to its proven safety in the various articles presented, which showed benefits mainly for those who wish to paternity. However, its therapeutic choice must be individualized considering the clinical context of the patient and its therapeutic target. It is emphasized the fact that the character of the research is not to exhaust all the literature about CC, but to provide subsidies for future investigations.

In short, it is extremely important that the positive and negative points regarding hypogonadism therapy are clarified prior to its indication, so that when indicating each treatment model, its risk-benefit ratios are exposed. Thereby, in TRT, it is necessary to clarify the damage to male fertility, already well documented in the literature, which can irreversibly compromise the gonadal axis and impair the intratesticular production of testosterone, in addition to the proposed cardiovascular effects, which still have a lack of studies. In the literature to confirm its losses [6,12].

On the other hand, it is necessary to clarify that this approach is currently considered the gold standard for the treatment of male hypogonadism by the Treaty of Clinical Endocrinology (Vilar) and brings with it obvious benefits in relation to muscle mass, bone mass, libido and in several other aspects by its ability to raise total testosterone to supraphysiological levels1. With regard to CC, its relationship with the desire for fertility and its therapeutic safety both in the short and long term must be clearly established, since when starting this therapy there will be no inhibition of the HHG axis, as on testosterone [6].

Thus, its action will act by inhibiting the negative feedback by estrogen, which is elevated in patients with increased adiposity, boosting the stimulus to the production of gonadotropins, with a consequent increase in both free and intratesticular testosterone, thus perpetuating spermatogenesis and raising serum testosterone levels, at physiological levels [1,5,18,20].

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litle	Authors	Year	Journal	Ojective
Treatment of Men with Central Hypogonadism: Alternatives for Testosterone Replacement Therapy	Ide V; Vanderschueren D; Antonio L;	2020	International journal of molecular sciences - Volume 22	Address the pharmacology of each therapeutic model for hypogonadism, whether within the guidelines or OFF label, as is the case with Clomiphene Citrate. Its purpose is to analyze risk-benefit in the use of each therapy and also address alternative therapies, even non- pharmacological ones.
Effect of clomiphene citrate treatment or the Sertoli cells of dysmetabolic obese men with low testosterone levels	n Pelusi C, et al.	2020	Clin Endocrinol (Oxf)	Prove that Clomiphene Citrate (CC) restores the hypothalamic-pituitary-gonadal (HPG) axis by increasing total testosterone (TT) levels to physiological levels in patients with dysmetabolic conditions such as obesity, metabolic syndrome and type 2 diabetes mellitus (DM2).
Impact of Clomiphene Citrate on the Steroid Profile in Dysmetabolic Men with Low Testosterone Levels	Pelusi C, et al.	2021	Horm Met Res	To evaluate the response of clomiphene citrate in dysmetabolic patients with low free testosterone profile. Analyzes a placebo group and another with the use of CC through a randomized study.
Clomiphene citrate improved testosterone and sperm concentration in hypogonadal males.	Delu A, Kiltz RJ, Kuznetsov VA, Trussell JC.	2020	Syst Biol Reprod Med	Clarify and consider clinical benefits in the use of CC. The study raises the possibility of considering empirical medical management (EMT) options for men with unexplained infertility (UI), in which clomiphene citrate (CC) has been shown to positively influence sperm parameters in hypogonadal men.
Testosterone Replacement Therapy Versus Clomiphene Citrate in the Young Hypogonadal Male.	Scovell JM, Khera M.	2018	EurUrol Focus	Discuss the risks and benefits of treatment options available to the young patient with hypogonadism, for whom future fertility is an important consideration. Also demonstrate therapeutic alternatives, such as clomiphene citrate and human chorionic gonadotropin.
Long-Term Safety and Efficacy of Clomiphene Citrate for the Treatment of Hypogonadism.	Krzastek SC, et al.	2019	J Urol	To evaluate improvements in testosterone and hypogonadism symptoms during prolonged use of Clomiphene Citrate.
Management of Endocrine Disease:	Lapauw B,	2020	Eur J Endocrinol	Discuss the interference of obesity in the

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Rationale and current evidence for testosterone therapy in the management of obesity and its complications.	Kaufman JM.			condition of hypogonadism, so that reduced serum levels of Testosterone have a proven negative effect on proper body formation
Medical Treatments for Hypogonadism do not Significantly Increase the Risk of Deep Vein Thrombosis Over General Population Risk.	Kavoussi PK; Machen GL; Wenzel JL; Ellis AM; Kavoussi M; Kavoussi KM; Kavoussi SK;	2020	Urology, Volume 124	To compare the risk of vascular events in patients undergoing treatment with Testosterone and Clomiphene Citrate. A clear relationship was not established, as patients with DVT had other identifiable etiologies as a risk factor.
Pre-treatment estradiol does not predict testosterone response to clomiphene citrate.	Masterson JM; Cohen J; Blachman- Braun R; Machen GL; Sandlow J; Ramasamy R;	2020	Translational andrology and urology - Volume 9, Capitulo 2	Evidence of predictors for a good therapeutic response prior to the use of CC. In this study, it was proved that the low levels of gonadotropin have a strong correlation with a satisfactory response with Citrate.
Management of Anabolic Steroid- Induced Infertility: Novel Strategies for Fertility Maintenance and Recovery.	Tatem, AJ; et al.	2019	World J Mens Health	To demonstrate that the administration of exogenous testosterone, the gold standard for the management of hypogonadal patients, almost universally impairs spermatogenesis and may even completely eradicate it in some men.
Clinical and biochemical correlates of hypogonadism in men with type 2 diabetes mellitus.	Musa E, El- Bashir JM, Sani- Bello F, Bakari AG.	2021	Pan Afr Med J.	To determine clinical and biochemical correlates of hypogonadism and clinical predictors of low total testosterone levels in men with T2DM.
Enclomiphene citrate: A treatment that maintains fertility in men with secondary hypogonadism.	Earl, JA; Kim, ED;	2019	Expert Rev Endocrinol Metab - Volume 14 3 Edição	To characterize the pharmacology of clomiphene citrate and its androgenic effects.
Clomiphene Citrate for the Treatment of Hypogonadism.	Wheeler, KM; et al.	2019	Sex Med Rev	Demonstrate benefits to the use of CC, such as improvement in erectile function and bone mineral density, as well as a reduction in body mass index.
The use of selective estrogen receptor modulators on bone health in men.	Wong SK; et al.	2019	Aging Male	The article demonstrates the benefits of improving bone mineral density parameters through the use of clomiphene citrate as a therapeutic alternative to Testosterone Hormone Replacement Therapy.
European Academy of Andrology (EAA) guidelines on investigation, treatment and monitoring of functional hypogonadism in males: Endorsing organization: European Society of Endocrinology.	Corona, G; et al.	2020	Andrology - Volume 8, Capítulo 5	Update European Academy of Andrology (EAA) guidelines on functional hypogonadism.
Clomiphene citrate: A potential alternative for testosterone therapy in hypogonadal males.	Huijben, M; Lock, MTWT; de Kemp, VF;	2023	Endocrinol Diabetes Metab - Volume 6, Capítulo 3	To evaluate the safety and efficacy of long-term clomiphene citrate (CC) treatment. No important clinical alteration was evidenced. Considered safe and effective for long-term therapy.

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