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Selective modulation of estrogen receptor in obese men with androgen deficiency: A systematic review and meta-analysis

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Abstract

Background: Although selective estrogen receptor modulators have been proposed as a treatment for men with central functional hypogonadism, only a few data have been produced in men with obesity-related functional androgen deficiency.

Objective: To determine whether and to what extent selective estrogen receptor modulators are an effective and safe therapy in men with obesity-related functional androgen deficiency.

Materials and methods: A thorough search of PubMed, Web of Science, Scopus, and Cochrane Library databases was performed to identify studies comparing testosterone levels before and after treatment. Mean differences with 95% coefficient intervals were combined using random effects models. Funnel plot, Egger's test, and trim-and-fill analysis were used to assess publication bias.

Results: Seven studies met the inclusion criteria providing information on 292 men with obesity-related functional androgen deficiency treated with clomiphene citrate (12.5–50 mg daily) or enclomiphene citrate (12.5–25 mg daily) for 1.5–4 months. The pooled estimates indicated a significant increase in testosterone levels both with clomiphene (mean difference: 11.56 nmol/L; 95% coefficient interval: 9.68, 13.43; I^2 = 69%, $p_{\text{for heterogeneity}}$ = 0.01) and enclomiphene citrate (mean difference: 7.50 nmol/L; 95% coefficient interval: 6.52, 8.48; I^2 = 4%, $p_{\text{for heterogeneity}}$ = 0.37). After the exclusion of one study on severely obese men, who exhibited the highest response rate to clomiphene citrate, the heterogeneity disappeared (mean difference: 10.27 nmol/L; 95% coefficient interval: 9.39, 11.16; I^2 = 0%, $p_{\text{for heterogeneity}}$ = 0.66). No publication bias was revealed by Egger's test and trim-and-fill analysis. No treatment-related unexpected findings regarding safety profile were registered.

Discussion and conclusion: Treatment with clomiphene citrate and enclomiphene citrate may be an effective and safe alternative to testosterone replacement therapy

in men with obesity-related functional androgen deficiency. Further long-term studies are warranted to define clinical reflections of the selective estrogen receptor modulators-induced increase in testosterone levels and to better clarify the safety profile.

KEYWORDS
clomiphene, enclomiphene, hypogonadism, metabolic syndrome, testosterone

1 | INTRODUCTION

Male hypogonadism is a clinical and biochemical syndrome due to testosterone (T) deficiency with the potential to deeply affect many physiological functions and impact quality of life.[1] Common symptoms of adulthood-onset hypogonadism include sexual dysfunctions (e.g., erectile dysfunction, decreased libido, and reduced spontaneous nocturnal/morning erections), fatigue, decreased concentration, sweating, and depressed mood.[1–4]

Hypogonadism can be classified according to the level of alteration in the hypothalamic-pituitary-gonadal (HPG) axis: primary hypogonadism is the most common cause of hypogonadism and results from direct testicular failure, whereas in secondary hypogonadism testes are inadequately stimulated by gonadotropins, resulting in androgen deficiency (AD), with a reduced or inappropriately normal serum concentration of gonadotropins.[1,3,5] Alternative classifications are based on the time of onset of symptoms (e.g., late-onset hypogonadism) or their potential reversibility. "Organic hypogonadism" refers to an irreversible condition due to a congenital or acquired disorder occurring at any level of the HPG axis,[6,7] whereas "functional hypogonadism" represents a potentially reversible alteration resulting from a dysregulation of the endocrine axis feedback mechanisms. A functional AD occurs more often with advancing age in the presence of comorbidities such as obesity and metabolic syndrome, clinical conditions associated with increased cardiovascular risk that worsen overall health status.[6–12] Because obesity has an increasing prevalence worldwide, it currently represents the comorbid state most often involved in the genesis of functional hypogonadism irrespective of age.[6,14]

T replacement therapy (TRT) is the first-choice treatment for men with hypogonadism.[5,15] Nevertheless, in some settings, TRT is not free from potential adverse effects, especially on cardiovascular and prostatic outcomes and it is contraindicated in hypogonadal men who are currently trying to conceive.[16–20] In functional AD, the use of selective estrogen receptor modulators (SERMs) may be an alternative therapy strategy to TRT.[21] In the central nervous system, SERMs exert antagonistic activities on estrogen receptors, thus inhibiting estrogen-negative feedback to the hypothalamus/pituitary gland. This effect results in an increased release of gonadotropins that stimulate T biosynthesis.[22] From a pathophysiological point of view, patients with an obesity-related functional AD (ORFAD) may represent ideal candidates for SERMs, as in the presence of fat mass excess, relative hyperestrogenism is generated that plays a pivotal role in determining AD.[23,24] Furthermore, advantages of SERMs over TRT include oral administration, maintenance of fertility, avoidance of T supraphysiologic levels,[21] and a reported lower risk of erythrocytosis.[25] Although SERMs have been proposed as a treatment for men with central hypogonadism,[26–30] their use is off-label, the evidence supporting their efficacy on hypogonadism symptoms is lacking and only a few data have been produced in obese men with AD.

The aim of this meta-analysis is to determine whether and to what extent SERMs are an effective and safe therapeutic option in men with ORFAD.

2 | MATERIALS AND METHODS

This meta-analysis was conducted according to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA).[31] It also complied with the guidelines for Meta-Analyses and Systematic Reviews of Observational Studies (MOOSE).[32] PRISMA and MOOSE Checklists have been presented in Tables S1 and S2, respectively. The study protocol was registered in the international prospective registry for systematic reviews with the registration number: CRD42022303958.

2.1 | Systematic search strategy

A systematic search was performed in PubMed, Web of Science, Scopus, and Cochrane Library, including the following free and vocabulary terms: "functional hypogonadism", "secondary hypogonadism" "central hypogonadism", "testosterone", "androgen*", "androgen deficiency", "SERM*", "selective estrogen receptor modulator*", "clomiphene", "enclomiphene", "tamoxifen", using the Boolean functions AND/OR. The search was restricted to English-language studies enrolling human participants, published up to September 2022. If it was not clear from the abstract whether the study contained relevant data, the full text was retrieved. The identification of eligible studies was performed by two authors independently (Daniele Tienforti and Francesca Di Giulio), and disagreements were resolved by the other investigators. The reference lists of the identified papers were also scrutinized for possible additional pertinent studies.

2.2 | Inclusion/exclusion criteria

The outcome of interest was the increase in T levels in response to treatment with SERMs. The eligibility criteria for selection were as

follows: (i) Studies conducted on obese men (body mass index [BMI] > 30 Kg/m^2), aged 18 years or older with low T levels who underwent therapy with SERMs; (ii) availability of pre- and post-treatment mean values ± SDs of T levels. Duplicates were rigorously checked and removed. We excluded studies with missing/incomplete or equivocal data, studies with no relevant design, studies enrolling non-obese populations or men with organic forms of AD, studies lacking to assess the outcome of interest, as well as commentaries/letters to the editor, meta-analyses and reviews. Two independent reviewers (Daniele Tienforti and Maria Totaro) evaluated the full text of all selected studies to determine eligibility, and any disagreements were resolved by a third reviewer (Arcangelo Barbonetti).

2.3 | Data extraction

Data were extracted from the selected articles by including the first author, publication year, country, study design, type, doses and duration of intervention, number, age, and baseline BMI of participants, and pre- and post-treatment mean values ± SD of circulating T levels. When available, additional information was registered, including post-treatment BMI, estradiol (E2), luteinizing hormone (LH) levels, seminal data, as well as any possible adverse effect registered during the treatment.

2.4 | Quality assessment

The methodological quality of included studies was assessed using the Effective Public Health Practice Project Quality assessment tool (EPHPP).[33] This tool is used to evaluate a variety of intervention study designs such as RCTs, before-and-after and case-control studies. This tool has been judged suitable to be used in systematic reviews of effectiveness and has been reported to have content and construct validity.[34] The tool assesses six domains: selection bias, study design, confounders, blinding, data collection method, and withdrawals/dropouts. Each domain is rated as strong, moderate, or weak; the global rating is rated "strong" if no weak rating was given, "moderate" if only one weak rating, and "weak" if two or more weak ratings were made. The evaluation was performed independently by three reviewers (Daniele Tienforti, Gilda Dalmazio, and Luca Spagnolo), involving a fourth reviewer (Chiara Castellini) to solve any discrepancies in judgment.

2.5 | Statistical analysis

The effect of SERMs in increasing androgen levels was assessed using the mean difference (MD) with a 95% coefficient interval (CI) between post-treatment and baseline T values with Mantel-Haenszel estimates. The Cochran's χ^2 (Cochran's Q) and I^2 tests were carried out to analyze statistical heterogeneity between the results of different studies: $I^2 > 50\%$ and/or $p < 0.05$ indicated substantial heterogeneity. Data were combined using a random effects model. Even when a low heterogeneity is detected, a random-effects model should be applied, because the validity of tests for heterogeneity can be limited with a small number of component studies. Publication bias was explored through the funnel plot[35] and Egger's test.[36] To correct for possible publication bias, Duval and Tweedie's 'trim-and-fill' analysis was also carried out.[37] Data were analyzed using the Review Manager of the Cochrane Library (version 5.3; The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark) and the R statistical software (version 3.6.3, 2020; The R Foundation for Statistical Computing, Vienna, Austria) with the "metafor" package.

3 | RESULTS

3.1 | Selection of studies

The electronic search yielded a total of 105 articles. After the removal of duplicates, 63 articles were obtained, of which 29 were excluded, because they were deemed irrelevant based on title and/or abstract reading. Thus, as shown in Figure 1, a total of 34 articles were identified, of which seven met the inclusion criteria.[14,38–42] Five studies assessed the effects of clomiphene citrate (CC)[14,38–40,42] and two studies the effects of enclomiphene citrate (EC).[41,42] Study design was interventional in five studies[38,39,41,42] and observational in two studies.[14,40] The biochemical criterion for AD was total T (tT) ≤ 10.4 nmol/L in five studies,[38,40–42] and ≤ 12.0 nmol/L in two studies.[14,39] Details of the main characteristics of the articles included in the quantitative analysis are shown in Table 1.

3.2 | Quality of included studies

The quality assessment, based on the EPHPP, is presented in Table 2. Overall, three studies received a methodological quality rating of strong,[39,41,42] and four studies of moderate quality.[14,38,40,42] The "data collection method" and "confounders" items received the highest rating among the studies; on the contrary, the item "blinding" was the most lacking, as only in three studies, participants and research staff who assessed outcomes were blind to the study conditions.

3.3 | Summary of results

Overall, the studies included gave information about 292 obese men with AD treated with CC (12.5, 25, or 50 mg daily)[14,38–40,42] or EC (12.5 or 25 mg daily)[41,42] with a follow-up ranging from 1.5 to 4 months. The mean increase in tT levels ranged from 6.80[42] to 16.10 nmol/L,[42] resulting in a significant pooled MD of 9.77 nmol/L (95% CI: 8.22, 11.31; $p < 0.00001$) with significant heterogeneity ($I^2 = 80\%$, $p_{\text{for heterogeneity}} < 0.00001$) (Figure 2).

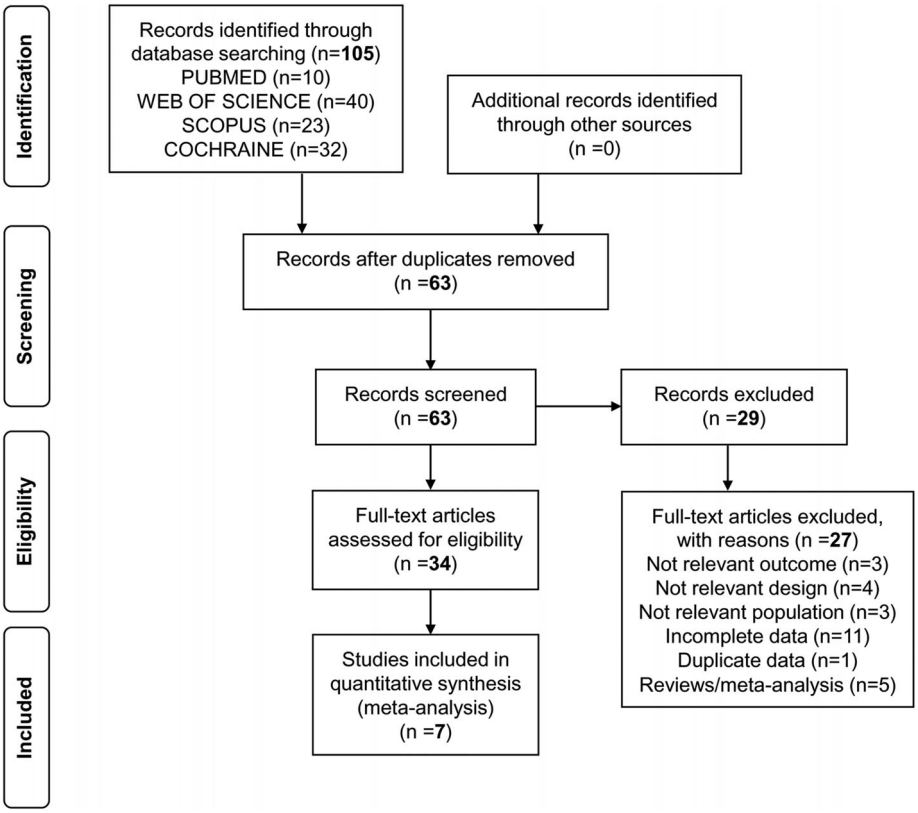

FIGURE 1 Flow diagram showing an overview of the study selection process

Similar results were produced when the analysis was restricted to the intervention studies[38,39,41,42] (pooled MD: 9.57 nmol/L, 95% CI: 7.57, 11.58; $p < 0.00001$. $I^2 = 83\%$, $p_{\text{for heterogeneity}} < 0.00001$).

3.4 | Analysis of heterogeneity

In order to identify possible sources of the between-study heterogeneity, a subgroup analysis was performed by type of SERM. When studies with CC and those with EC were considered separately, pooled estimates demonstrated a significant increase of tT levels under CC treatment (MD: 11.56 nmol/L; 95% CI: 9.68, 13.43; $p < 0.00001$), albeit persisting significant heterogeneity ($I^2 = 69\%$, $p_{\text{for heterogeneity}} = 0.01$) (Figure 3A). The exclusion of the study by Soares et al.,[42] carried out in severely obese men, who exhibited the highest response rate to CC (Figure 3B), resulted in a negligible effect on a pooled estimate (MD: 10.27 nmol/L; 95% CI: 9.39, 11.16; $p < 0.00001$), while abolishing heterogeneity ($I^2 = 0\%$, $p_{\text{for heterogeneity}} = 0.66$). On the contrary, when a sub-group analysis was restricted to the three studies that used CC at the same dosage of 50 mg daily,[38,39,42] a large and significant heterogeneity persisted (MD: 12.42 nmol/L; 95% CI: 9.04, 15.79; $p < 0.00001$; $I^2 = 76\%$, $p_{\text{for heterogeneity}} = 0.02$).

The subgroup analysis on EC (Figure 3A) showed a significant increase in tT levels (MD: 7.50 nmol/L; 95% CI: 6.52, 8.48; $p < 0.00001$) in the absence of significant heterogeneity ($I^2 = 4\%$, $p_{\text{for heterogeneity}} = 0.37$).

3.5 | Publication bias

Although the asymmetry of the funnel plot could suggest a possible publication bias (Figure S1), the degree of asymmetry was not significant at the Egger's test ($p = 0.79$), and the trim-and-fill analysis did not identify putative missing studies.

4 | DISCUSSION

In the present meta-analysis, the therapy with SERMs, CC and EC, in a population of obese men with functional AD resulted in a significant increase in circulating tT levels in the absence of major treatment-related side effects. To our knowledge, this is the first meta-analysis published so far on the efficacy and safety of SERMs in men with ORFAD. Under treatment with SERMs from 1.5 to 4 months, levels of tT rose by an average of about 10 nmol/L. Interestingly, results from sub-group analyses did not seem to support the claimed greater efficacy of EC compared to CC,[30] at least in obese patients. In fact, at the sub-group analysis, dividing the studies according to the molecules used, the overall mean increase in tT was 11.56 nmol/L with CC and 7.50 nmol/L with EC. The two isomers of CC are EC and zuclomiphene: the fact that EC appeared to be less effective than CC suggested a possible major contribution of the other CC isomer, zuclomiphene, a hypothesis that deserves to be confirmed by further targeted studies.

TABLE 1 Main characteristics of the included studies

Study	Country	Study Design	Intervention	Patients (*n*)	Mean age (years)	Mean baseline BMI (kg/m^2)	Mean BMI post (kg/m^2)	tT values inclusion criteria (nmol/L)	Mean E2 levels (pg/ml)	Mean LH levels (mUI/ml)	Semen parameters	Adverse effects
Bendre et al., 2015[14]	USA	Obs	CC 12.5 mg daily for 3 months	11	NA	35.2 ± 4.8	35.9 ± 4.6	T ≤ 12.0	NA	3.3 ± 5.7		Mild rash: *n* = 1 Acne: *n* = 3 Irritability: *n* = 3
Habous et al., 2018[38]	Saudi Arabia	Int	CC 50 mg daily for 3 months	90	42 ± 10	30.8 ± 6.2	30.4	T ≤ 10.4	NA	NA		NA
Helo et al., 2015[39]	USA	Int	CC 50 mg daily for 3 months	12	33 ± 4	32.0 ± 7.5	NA	T ≤ 12.0	27.6 ± 3.2	3.9 ± 1.8	Baseline versus post-intervention semen volume (ml): 2.7 ± 0.3 versus 2.2 ± 0.5 (p = 0.4) Baseline versus post-intervention sperm count (x 10^6/ml): 32 ± 12 versus 41 ± 13 (p = 0.6) Baseline versus post-intervention sperm motility (%): 28.0 ± 5.0 versus 41.0 ± 5.4 (p = 0.08)	No major reported
Helo et al., 2017[40]	USA	Obs	CC 25 mg daily for at least 1.5 months	15	41 ± 14	31.4 ± 5.5	NA	T ≤ 10.4	17.0 ± 11.4	5.8 ± 3.1		NA

(Continues)

TABLE 1 (Continued)

Study	Country	Study Design	Intervention	Patients (*n*)	Mean age (years)	Mean baseline BMI (kg/m^2)	Mean BMI post (kg/m^2)	tT values inclusion criteria (nmol/L)	Mean E2 levels (pg/ml)	Mean LH levels (mUI/ml)	Semen parameters	Adverse effects
Kim et al., 2016a[a 41]	USA	Int	EC 12.5 mg daily for 4 months	41	49 ± 7	33.1 ± 4.4	NA	T ≤ 10.4	NA	4.0	Baseline sperm count: 98.0 ± 87.2 × 10^6/ml Mean change in sperm count after treatment: +11.7%	↑ Triglycerides: *n* = 1 Ischemic stroke: *n* = 1 Anxiety: *n* = 1
Kim et al., 2016b[a 41]	USA	Int	EC 25 mg daily for 4 months	44	47 ± 9	33.8 ± 4.6	NA	T ≤ 10.4	NA	4.0	Baseline sperm count: 79.0 ± 55.2 × 106/ml Mean change in sperm count after treatment: +15.2%	↑ PSA levels[b] ↑ Hematocrit[b]
Soares et al., 2018[42]	Brazil	Int	CC 50 mg daily for 3 months	35	36 ± 8	45.5 ± 11.3	47.7 ± 9.0	T ≤ 10.4	32.5 ± 12.6	4.3 ± 1.8		No major reported
Wiehle et al., 2014a[a 42]	USA	Int	EC 12.5 mg daily for 3 months	25	50 ± 12	32.6 ± 5.2	NA	T ≤ 10.4	20.8 ± 12.4	4.4 ± 1.8	Men with sperm count < 15 × 106/ml (baseline vs. post-intervention): 19.0% versus 12.5%	NA
Wiehle et al., 2014b[a 42]	USA	Int	EC 25 mg daily for 3 months	32	49 ± 11	31.7 ± 4.9	NA	T ≤ 10.4	24.7 ± 15.9	5.4 ± 4.0	Men with sperm count < 15 × 106/ml (baseline vs. post-intervention): 5.0% versus 0.0%	NA

Abbreviations: BMI, body mass index; CC, clomiphene citrate; E2, estradiol; EC, enclomiphene citrate; Int, intervention study; LH, luteinizing hormone; NA, not available; Obs, observational study; tT, total testosterone.

[a]These studies reported data on two treatment arms with different doses of EC.

[b]These effects resulted in treatment discontinuation.

TABLE 2 Quality assessment of the included studies: effective public health practice project (EPHPP) checklist

Study	Selection bias	Study design	Confounders	Blinding	Data collection method	Withdrawal and dropout	Total score
Bendre et al., 2015[14]	Moderate	Moderate	Strong	Weak	Strong	Strong	Moderate
Habous et al., 2018[38]	Strong	Strong	Strong	Weak	Strong	Strong	Moderate
Helo et al., 2015[39]	Strong	Strong	Strong	Strong	Strong	Strong	Strong
Helo et al., 2016[40]	Moderate	Moderate	Strong	Weak	Strong	Strong	Moderate
Kim et al., 2016[41]	Strong	Strong	Strong	Strong	Strong	Strong	Strong
Soares et al., 2018[42]	Strong	Strong	Strong	Strong	Strong	Strong	Strong
Wiehle et al., 2014[42]	Strong	Strong	Strong	Moderate	Strong	Weak	Moderate

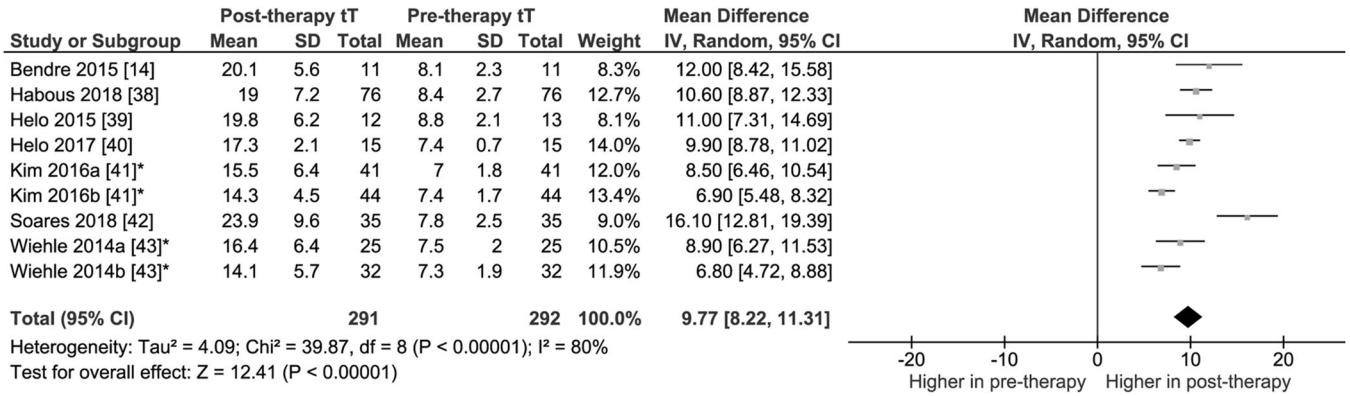

FIGURE 2 Effect of selective estrogen receptor modulators on testosterone levels in obese men with androgen deficiency. Forest plot depicting the mean difference in circulating total testosterone (tT) levels from baseline after a 1.5–4-month treatment with clomiphene or enclomiphene citrate. The diamond indicates the overall summary estimate and the width of the diamond represents the 95% confidence interval (CI); boxes indicate the weight of individual studies in the pooled result. df, degrees of freedom; IV, inverse variance; SD, standard deviation

In a recent meta-analysis,[43] published during the writing of the present study, CC therapy in hypogonadal patients was associated with a significant increase in tT levels compared with baseline. However, in that study, any conclusion was hindered by the high and not investigated heterogeneity. As a partial explanation of such a wide and significant between-study variability in results, no specific selection criteria for hypogonadal patients were used. On the contrary, in our meta-analysis, the inclusion of studies only enrolling patients with ORFAD resulted in aggregate sub-group estimates not burdened by heterogeneity.

Our selection criterion has a strong pathophysiological basis. Indeed, accumulation of fat mass is associated with aromatization of T to E2,[44] resulting in the inhibition of gonadotropin secretion by estrogen-negative feedback[23,24] and lower T levels. The decrease in follicle-stimulating hormone (FSH) and LH levels results in functional impairment of both spermatogenesis and steroidogenesis, with lower T biosynthesis. The clinical relevance of these pathophysiological mechanisms is demonstrated by the well-documented linear relationship between weight loss in obese men and increased circulating T levels.[6] The role of estrogens in inhibiting gonadotropin secretion underlies the rationale for the use of SERMs as a treatment option for ORFAD. In this view, the greatest increase in androgen levels could be achieved where more severe obesity is associated with a deeper estrogen-dependent suppression of gonadotropins, resulting in more severe AD. Accordingly, in our analysis, the significant heterogeneity among the studies included in the overall analysis was completely abolished in the sub-group analysis after the exclusion of the study by Soares et al.[42] Interestingly, this latter study enrolled severely obese men with a mean BMI of 45.5 ± 11.3 kg/m^2; this population exhibited the highest levels of circulating E2 (Table 1) and as expected, reported the highest increases in tT levels under CC therapy, thus explaining the heterogeneity of the overall estimate.

Noteworthy, based on the above mechanism of action, unlike TRT, which is contraindicated in hypogonadal patients who are currently trying to conceive,[16] SERMs therapy promotes LH and FSH secretion, and therefore it supports spermatogenesis meanwhile stimulating T biosynthesis. This property is the reason why SERMs are often used as post-cycle therapy by anabolic androgen steroids abusers, in attempts to recover the HPG axis suppressed by supraphysiological doses of androgens.[45] Interestingly, in all three studies that provided information on semen parameters, treatment with CC[39] or EC[41,42] was associated with improvements in semen quality (Table 1). Another clinically relevant aspect of treatment with SERMs in ORFAD is the safety profile. In fact, while considering the limitations of the short follow-up,

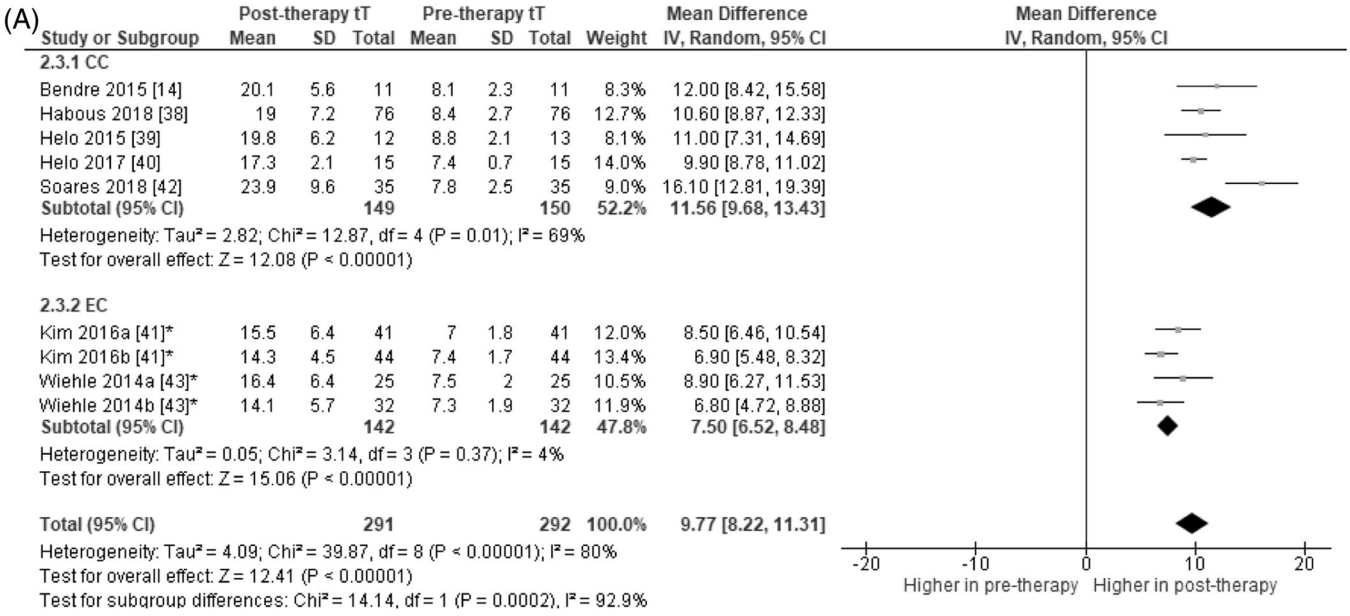

FIGURE 3 Effect of selective estrogen receptor modulators (SERMs) on testosterone levels in obese men with androgen deficiency: analysis of heterogeneity. (A) Sub-group analysis by type of SERM, clomiphene citrate (CC), and enclomiphene citrate (EC). (B) Effect of CC after the exclusion of the study by Soares et al.,[42] enrolling severely obese men. The forest plots depict the mean difference in circulating total testosterone (tT) levels from baseline after a 1.5–4-month treatment with SERMs. Diamonds indicate the overall summary estimates and the width of the diamonds represents the 95% confidence interval (CI); boxes indicate the weight of individual studies in the pooled results. df, degrees of freedom; IV, inverse variance; SD, standard deviation

no unexpected findings regarding the safety profile were reported in the studies included (Table 1). While changes in prostate-specific antigen and hematocrit are secondary to increases in T levels, other events were considered to not be related to treatment. In the study by Kim et al.,[41] a case of ischemic stroke was registered in the EC 12.5 mg arm. Indeed, after a relatively short treatment with EC (34 days), this patient had not developed significant changes in hemoglobin levels, but he had an obvious, preexisting high-risk profile for stroke: he was severely dyslipidemic, obese, diabetic, with sleep apnea and untreated atrial fibrillation. Because of the high number of risk factors and limited exposure to treatment, the authors concluded that it was highly unlikely that EC was the cause of the stroke.[41]

This meta-analysis has some limitations. First, hypogonadism represents a clinical and biochemical syndrome.[1] Unfortunately, the lack of information on symptoms and signs of AD before and after treatment makes it impossible to determine whether the enrolled patients were clinically hypogonadal at baseline and whether they derived any clinical benefit from treatment other than the biochemical increase in tT levels. However, it should be recalled that in functional hypogonadism, T levels are often not unequivocally low, but rather in the borderline range fluctuating around the lower limit of normal.[6] Therefore, any treatment (weight loss, lifestyle change, and optimization of comorbidity status) that results in even a modest increase in T may be sufficient to normalize its circulating levels, breaking down the biochemical criterion of hypogonadism, regardless of the presence of symptoms and signs. Second, the limited number of studies hindered sub-group analyses and/or meta-regressions to assess the dose-response effects of SERMs in increasing T levels. Third, the short follow-up is insufficient to define both the safety and clinical efficacy of the treatment on most endpoints. Despite the short follow-up, it cannot be ruled out that enrolled patients achieved a weight loss that could significantly contribute to the increase in tT. This would make it difficult to define the actual impact of SERMs treatment on increasing androgen levels. However, only in one of the studies in which anthropometry was re-evaluated after treatment,[38] authors reported a decrease in BMI with respect to the baseline (Table 1). Finally, due to the relationships between insulin resistance and sex hormone-binding globulin, free T levels would undoubtedly be more informative than total T in

ORFAD. Unfortunately, free T levels were reported in three studies only,[39,40,42] thus hindering the statistical power of the quantitative synthesis. What is more, only one out of the three studies[42] provided the values of calculated free T, a more reliable measure than direct enzyme immunoassays[46]. As expected, in that study on severely obese patients, low levels of calculated free T were found (mean value: 52 ± 16 pg/ml).

In conclusion, treatment with SERMs, particularly CC, may be an effective and safe alternative to TRT, in specific categories of patients, such as men with ORFAD, where levels of tT can rise by an average of about 10 nmol/L from baseline. Further studies with long follow-ups are warranted to define the clinical relevance of the SERMs-induced increase in tT on hypogonadism features and to better clarify the safety profile.

AUTHOR CONTRIBUTIONS

Daniele Tienforti and Francesca Di Giulio identified eligible studies. Daniele Tienforti, Maria Totaro, and Arcangelo Barbonetti evaluated the full text of all selected studies to determine eligibility. Daniele Tienforti and Chiara Castellini performed data extraction from the selected studies. Daniele Tienforti, Gilda Dalmazio, Luca Spagnolo, and Chiara Castellini assessed the methodological quality of the studies. Arcangelo Barbonetti, Daniele Tienforti, and Mario Muselli performed the statistical analysis. Daniele Tienforti and Arcangelo Barbonetti wrote the manuscript. Giovanni Corona and Marco Giorgio Baroni critically revised the manuscript.

DATA AVAILABILITY STATEMENT

The authors confirm that the data supporting the findings of this study are available within the article and its supplementary materials.

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