SEXUAL MEDICINE REVIEWS REVIEWS

Efficacy of Non-Testosterone–Based Treatment in Hypogonadal Men: A Review

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ABSTRACT

Introduction: Although testosterone replacement therapy is an effective treatment for hypogonadism, there are safety concerns regarding potential cardiovascular risks and fertility preservation.

Objective: To assess the effect of selective estrogen receptor modulator (SERM), aromatase inhibitor, and human chorionic gonadotropin (hCG) on total testosterone (TT) levels and hypogonadism.

Methods: We performed a systematic literature review from 1987 to 2019 via PubMed, Cochrane review, and Web of Science. Terms used were *infertility*, *hypogonadism*, *alternative to testosterone therapy*, *selective estrogen receptor modulator*, *aromatase inhibitor,* and *human chorionic gonadotropin*. Studies that reported an effect of TT and hypogonadism after treatment of each medication were selected. Hypogonadal symptoms were assessed by the Androgen Deficiency of The Aging Male (ADAM) questionnaire. Aggregated data were analyzed via Chi-squared analysis.

Results: From literature, 25 studies were selected; of which, 12 evaluated efficacy of aromatase inhibitor, 8 evaluated SERMs, and 5 evaluated hCG effects. For SERMs, 512 patients with mean age 42.3 ± 1.94 years showed mean TT before treatment vs after treatment (167.9 ± 202.8 [ng/dl] vs 366.2 ± 32.3 [ng/dl], $P < .0001$ [180.5–216.1 95% confidence interval {CI}]). For aromatase inhibitor, 375 patients with mean age 54.1 ± 0.67 years showed mean TT before treatment vs after treatment (167.9 ± 202.8 [ng/dl] vs 366.2 ± 32.3 [ng/dl], $P < .0001$ [180.5–216.1 95% CI]). SERMs also showed ADAM before treatment vs after treatment (4.95 ± 0.28 vs 5.50 ± 0.19, $P < .0001$ [0.523–0.581 95% CI]). For hCG, 196 patients with mean age 41.7 ± 1.5 years showed mean TT before treatment vs after treatment (284.5 ± 13.6 [ng/dl] vs 565.6 ± 39.7 [ng/dl], $P < .0001$ [275.2–287.0 95% CI]). In addition, hCG also showed ADAM before treatment vs after treatment (28.1 ± 2.0 vs 30.9 ± 2.3, $P < .0001$ [2.313 95% CI]).

Conclusions: Non-testosterone therapies are efficacious in hypogonadal men. Our results show statistically significant improvement in TT and ADAM scores in all 3 medications after treatment. Future studies are warranted to elucidate the relationship between improved hypogonadism and erectile function in the setting of non-testosterone–based treatment. **Raheem OA, Chen TT, Le TV, et al. Efficacy of Non-Testosterone–Based Treatment in Hypogonadal Men: A Review. Sex Med Rev 2020;XX:XXX–XXX.**

Key Words: Hypogonadism; Male Infertility; Hormonal; Selective Estrogen Receptor Modulator; Aromatase Inhibitor; Human Chorionic Gonadotrophin

INTRODUCTION

Male hypogonadism is characterized by low serum testosterone and associated with symptoms such as decreased libido, erectile dysfunction (ED), loss of vitality, loss of lean muscle mass, fatigue, and depression.[1,2] The etiology of hypogonadism in the aging male is a combination of hypothalamic–pituitary–gonadal (HPG) axis dysfunction and primary testicular failure due to decreased production of testosterone by Leydig cells.[3] The incidence of hypogonadism in men aged 40–79 years varies from 2.1% to 5.7%.[4] The overall prevalence of male hypogonadism is reported to be 37% in the United States.[5,6] Criteria for a diagnosis of hypogonadism include the presence of abnormal sexual symptoms, total testosterone (TT) levels, and free testosterone levels.[7,8] Several societies used these 3 indicators to define male hypogonadism. The American

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Urological Association (AUA) guidelines suggest TT levels lower than 300 ng/dL on 2 independent tests with supported symptoms.[8] In addition, the Endocrine Society also defines male hypogonadism as a patient presenting with signs of testosterone deficiency and low serum TT and/or free testosterone laboratory values.[9]

Moreover, male hypogonadism can be subtyped into several different forms: primary, secondary, hypogonadotropic, and hypergonadotropic. Primary testosterone deficiency has been shown to be linked to testicular dysfunction. Associated disease states are Klinefelter syndrome, undescended testicles, mumps orchitis, and hemochromatosis. This is contrasted with secondary hypogonadism, which is linked to an issue with the pituitary or hypothalamus and is largely associated with Kallmann's syndrome. In addition, hypogonadism can be either hypogonadotropic or hypergonadotropic. Hypogonadotropic exhibits decreased follicle-stimulating hormone (FSH) and luteinizing hormone (LH) levels; hypergonadotropic disorder is when a patient presents with increased FSH and LH levels. In the clinical setting, it is important to identify the presenting patient's hypogonatic subtyped to offer the optimal treatment.[8,9]

Treatment for hypogonadism typically includes testosterone replacement therapy (TRT), which results in satisfactory amelioration of disease-specific symptoms and normalization of serum testosterone.[2] TRT improves sexual function, muscle strength, bone density, mood, and cognition of the patient. Improved symptoms depends on the pretreatment presentation, and results between patients can vary.[10] Although these benefits can significantly improve quality of life for hypogonadal men, TRT can affect spermatogenesis in some but not all men.[11] Sperm production depends on a functionally intact HPG axis with normal pituitary secretion of LH and FSH to support testicular testosterone production and spermatogenesis. Exogenous testosterone suppresses the HPG axis and testicular testosterone production.[12] A study by the World Health Organization found that 65% of men became azoospermic by 6 months, with an average time to azoospermia of 120 days.[13] Although 84% achieved normal sperm density after a median of 3.7 months after cessation of exogenous testosterone, only 46% of men recovered their pre-TRT baseline sperm density.[13] Notably, a 2010 survey of AUA member urologists found that 25% of patients believed that TRT would improve a man's fertility.[14] Patients' lack of awareness regarding potential reproductive risks of exogenous testosterone use and some physicians' inappropriate overprescription expose a need for improved education regarding medical management of male factor infertility.

The European Association of Urology and AUA guidelines have addressed the issue of fertility preservation in patients who present with hypogonadism.[2,11] The European Association of Urology guidelines support the use of human chorionic gonadotropin (hCG) in men with secondary hypogonadism who desire future fertility.[2] The AUA guidelines conditionally support the use of aromatase inhibitors (AIs), hCG, and selective estrogen receptor modulators (SERMs) for these men.[10] In addition, the 2018 Endocrine Society Clinical Practice Guidelines recommend against the use of exogenous testosterone in patients who desire fertility in the near term.[9] In accordance with the AUA guideline, hCG is the only drug that has been approved by the Food and Drug Administration specifically to treat males with hypogonadotropic hypogonadism.[10] The overall quantity and quality of studies investigating the use of these non-testosterone agents in men are limited. However, several studies provide important insight into the impact that SERMs, AIs, and hCG can have on the hypogonadal men's serum testosterone level, libido, and erectile function. Therefore, this study serves to highlight current data regarding alternative treatment options for men with hypogonadism who wish to preserve their fertility.

METHODS

We performed a comprehensive literature review from 1980 to 2019 via PubMed and Medline. The following subject heading terms were used: "male infertility," "hypogonadism," "alternative to testosterone therapy," "selective estrogen receptor modulators," "aromatase inhibitor," and "human chorionic gonadotrophin." Inclusion criteria were studies evaluating the efficacy of SERMs, AIs, and hCG in the treatment of hypogonadism through sequential measurements of serum androgens. In addition, an emphasis was placed on research that reported measurements of libidinal function. The most discriminative method for tracking libido used was the quantitative Androgen Deficiency in Aging Males (qADAM) score followed by the Androgen Deficiency in Aging Males (ADAM) score and finally subjective report of libido. The ADAM questionnaire is a 10-question validated questionnaire with *yes* and *no* answers focusing on key clinical features of hypogonadism. Every reply affirming a symptom with a "yes" answer is a point meaning that lower scores represent more significant symptoms associated with hypogonadism. The ADAM score does not incorporate the laboratory factors that go into the diagnosis of this disease. These laboratory values need to be tested injunction with the ADAM questionnaire. Recently, several studies have applied the qADAM questionnaire in treatment of male hypogonadism. This questionnaire consists of the 10 questions of the original ADAM but uses a Likert scale of 1 to 5 with 5 representing an absence of an associated symptom and 1 representing maximal symptom severity. The qADAM better quantifies a scale of improvement in symptoms associated with hypogonadism when full symptom resolution is not achieved, with scores ranging from 10 to 50. When available in reviewed studies, we attempted to collect ED data using the International Index of Erectile Function (IIEF) questionnaires. Observational and randomized control trials that fit the aforementioned criteria were included in this review. Study design type is specified in Tables 1–3 to allow the reader to determine the strength of each trial. Exclusion criteria were

Table 1. Summary of studies on clomiphene citrate effect on testosterone and hypogonadism

Authors (y)	Study design	Dose	N	Mean age (y)	Duration (Mo)	Mean T (ng/dL)		Mean T/E		Libido	ADAM/qADAM score	
						Before	After	Before	After		Before	After
Guay et al[18] (2003)	Retrospective single-arm observational study	50 mg every other day	173	54.3	4	Free T 9.3 pg/mL	Free T 21.2 pg/mL	NA	NA	NA	NA	NA
Taylor et al[19] (2009)	Retrospective cohort study	50 mg daily	42	42 (19–70)	23 (8–40)	277	573	NA	NA	Improved	4.9	2.1
Katz et al[20] (2011)	Prospective single-arm trial	25 to 50 mg every other day	86	29 ± 3 (22–37)	19 ± 14	192 ± 87	485 ± 165	7.4	12.4	Improved	5 (2–7)	2 (1–4)
Moskovic et al[21] (2011)	Population cohort study	25 to 50 mg every other day	46	44 ± 18	>12	228 ± 48	612 ± 212	6.1	12.8	NA	7 (5–9)	3 (5–7)
Ramasamy et al[22] (2014)	Retrospective cohort study	25 mg daily	31	40.9 ± 9.4	NA	247.0 ± 66.5	503.5 ± 306.8	12.4	25.2	NA	NA	35 (27–43)
Helo et al[35] (2015)	Randomized control trial	25 mg daily	13	33 ± 3.9	12 wk	253 ± 17	571 ± 51	9.3 ± 2.5	12 ± 1.3	NA	37 ± 1.9	40 ± 1.3
Chandrapal et al[23] (2016)	Prospective cohort study	50 mg daily or every other d	77	34 ± 6 (22 –51)	4	324 ± 194	530 ± 262	NA	NA	NA	4	3
Dadhich et al[24] (2017)	Prospective cohort study	50 mg daily or every other d	23	36.5 ± 8	3.5 ± 1.6	235.5 ± 63.2	438 ± 67.4	11.7	12.5	NA	3.5 ± 3	1.5 ± 1.9
Soares et al[25] (2018)	Randomized double-blind placebo-controlled trial	50 mg daily	34	36.5 ± 7.8	3	225.8 ± 72.5	687.9 ± 276.7	8.2	21.2	Improved	5.2 ± 2.6	3.38 ± 2.74
Habous et al[49] (2018)	Randomized control trial	50 mg daily	95	41.8 ± 10	3	243 ± 78	548 ± 209	NA	NA	NA	20.5 ± 3.8	NA

ADAM = Androgen Deficiency of The Aging Male; qADAM = quantitative Androgen Deficiency in Aging Males; NA = not available; T/E = testosterone/estrogen.

Table 2. Summary of studies on aromatase inhibitor effect on testosterone and hypogonadism

Authors (y)	Study design	Drug/Dose	N	Mean age (y)	Duration (Mo)	Mean T (ng/dL)		Mean T/E		Libido	ADAM/qADAM score	
						Before	After	Before	After		Before	After
Saylam et al[33] (2011)	Prospective single-arm study	Letrozole/2 mg daily	27	34.92 ± 6.66	6.59 ± 0.88	255 ± 23	527 ± 74	8 ± 0.4	39 ± 6.1	NA	NA	NA
Helo et al[35] (2015)	Randomized control trial	Anastrozole/1 mg daily	13	33 ± 3.9	12* wk	248 ± 18	408 ± 56	9.3 ± 2.5	17 ± 1.5	NA	36 ± 1.6	38 ± 1.3
Dias et al[38] (2016)	Double-blind randomized control trial	Anastrozole/1 mg daily	13	70 ± 1	12	272 ± 13	NA	NA	NA	NA	NA	NA
Shoshany et al[39] (2017)	Retrospective single-arm observational study	Anastrozole/1 mg daily	86	36 Median	4	258.4 ± 10.8	449.9 ± 19.5	6.98 ± .33	24.2 ± 3	NA	NA	NA
Leder et al[34] (2004)	Randomized double-blind placebo controlled trial	Anastrozole/1 mg daily	12	67 ± 3	12*wk	289 ± 37	572 ± 139	NA	NA	No change	NA	NA
Leder et al[34] (2004)	Randomized double-blind placebo controlled trial	Anastrozole/1 mg twice weekly	11	67 ± 3	12* wk	290 ± 50	520 ± 91	NA	NA	No change	NA	NA
Harden[37] (2003)	Case report	Letrozole/2.5 mg daily	1	61	8	187	754	NA	NA	Improved	NA	NA
Raman[32] (2002)	Prospective non-randomized study	Testolactone/50 to 100 mg BID	74	NA	6	277	411	5.3 ± 0.2	12.4 ± 1.2	NA	NA	NA
Raman[32] (2002)	Prospective non-randomized study	Anastrozole/1 mg daily	104	NA	4.7	295	445	7.14 ± 0.3	18.1 ± 1.0	5% of patients complained of decreased libido	NA	NA
Gregoriou[36] (2012)	Prospective non-randomized study	Letrozole/2.5 mg daily	15	NA	6	275 ± 29	495 ± 65	9 ± 0.2	36 ± 4.5	NA	NA	NA
Gregoriou[36](2012)	Prospective non-randomized study	Anastrozole/1 mg daily	14	NA	6	265 ± 25	513 ± 65	8 ± 0.5	34 ± 5.9	NA	NA	NA

ADAM = Androgen Deficiency of The Aging Male; qADAM = quantitative Androgen Deficiency in Aging Males; NA = not available; T/E = testosterone/estrogen.

Table 3. Summary of studies on human chorionic gonadotrophin effect on testosterone and hypogonadism

Authors (Year)	Study design	Dose	N	Mean age (Year)	Duration (Month)	Mean T ng/dL		Mean T/E		Libido	ADAM score	
						Before	After	Before	After		Before	After
Buvat et al[45] (1987)	Randomized double-blind placebo-controlled study	5000 IU twice per wk	45	22–63	1	609 ± 158	1060 ± 412	NA	NA	Improved	NA	NA
Tsujimura et al[42] (2005)	Prospective single-arm observational study	10,000 IU once per 2 wk	21	55.2 ± 6.4 (50–79)	8.0 ± 5.0 (3–24)	210 ± 50	270 ± 70	7.3	9.5	NA	NA	NA
Ishikawa et al[43] (2007)	Prospective single-arm observational study	5000 IU 3 times per wk	26	26 ± 12.6 (9–61)	25 (6–144)	42 ± 62	400 ± 330	3.2	21.9	NA	NA	NA
La Vignera et al[44] (2015)	Randomized control study	2000 IU twice per wk	10	50 (45–53)	6	198 (160–210)	318	7.9	12.2	NA	46.0 (43.0–49.0)	36
Habous et al[46] (2018)	Randomized control study	5000 IU twice per wk	94	41.8 ± 10.4	3	222 ± 59	467 ± 121	NA	NA	NA	20.5	NA

ADAM = Androgen Deficiency of The Aging Male; qADAM = quantitative Androgen Deficiency in Aging Males; NA = not available; T/E = testosterone/estrogen.

animal studies, studies involving children, female studies, and articles written in a language other than English. Aggregated data were analyzed via Chi-square analysis.

RESULTS

From the available literature, 25 studies were selected; of which, 12 studies evaluated efficacy of AIs, 8 evaluated SERMs, and 5 evaluated hCG effects. For SERMs, 512 patients with mean age 42.3 ± 1.94 years showed mean TT before treatment vs after treatment (167.9 ± 202.8 vs 366.2 ± 32.3, $P < .0001$ [180.5−216.1 95% confidence interval {CI}]). For AIs, 375 patients with mean age 54.1 ± 0.67 years showed mean TT before treatment vs after treatment (167.9 ± 202.8 vs 366.2 ± 32.3, $P < .0001$ [180.5−216.1 95% CI]). SERMs also showed ADAM before treatment vs after treatment (4.95 ± 0.28 vs 5.50 ± 0.19, $P < .0001$ [0.523−0.581 95% CI]). For hCG, 196 patients with mean age 41.7 ± 1.5 years showed mean TT before treatment vs after treatment (284.5 ± 13.6 vs 565.6 ± 39.7, $P < .0001$ [275.2−287.0 95% CI]). In addition, hCG also improved qADAM before treatment vs after treatment (28.1 ± 2.0 vs 30.9 ± 2.3, $P < .0001$ [2.313 95% CI]).

EVIDENCE SYNTHESIS OF THIS REVIEW

Selective Estrogen Receptor Modulators

SERMs are compounds that exhibit tissue-specific estrogen receptor (ER) agonist or antagonist activity. The functional diversity of SERMs reflects the molecular and functional complexity of the ER.[15] Four compounds make up the SERMs presently in clinical use in the United States: clomiphene citrate (CC), tamoxifen, toremifene, and raloxifene.[15] Each compound demonstrates a specific profile for its target tissue effects.[15] CC, now one of the most widely used drugs in the management of infertility, was approved by the Food and Drug Administration in 1967 for the treatment of ovulatory dysfunction in women desiring pregnancy (Clomid; Hoechst Marion Roussel or Serophene; Serono).[15] It is a triphenylethylene that is structurally related to tamoxifen and toremifene.[15] Notably, CC has been prescribed for more than 30 years off label, primarily by reproductive urologists, for men with idiopathic infertility and hypogonadism.[16] The AUA guidelines conditionally support the use of CC for hypogonadal men who desire to maintain fertility.[10] This section will review the biologic mechanism of action and relevant literature regarding the effects of CC on testosterone and hypogonadal function.

Biopharmacology and Mechanism of Action

CC binds to nuclear ER for prolonged periods of time and leads to a reduction in ER concentration by inhibiting normal ER replacement.[17] It blocks the normal negative feedback of circulating estradiol on the hypothalamus, preventing estrogen from lowering the output of gonadotropin-releasing hormone

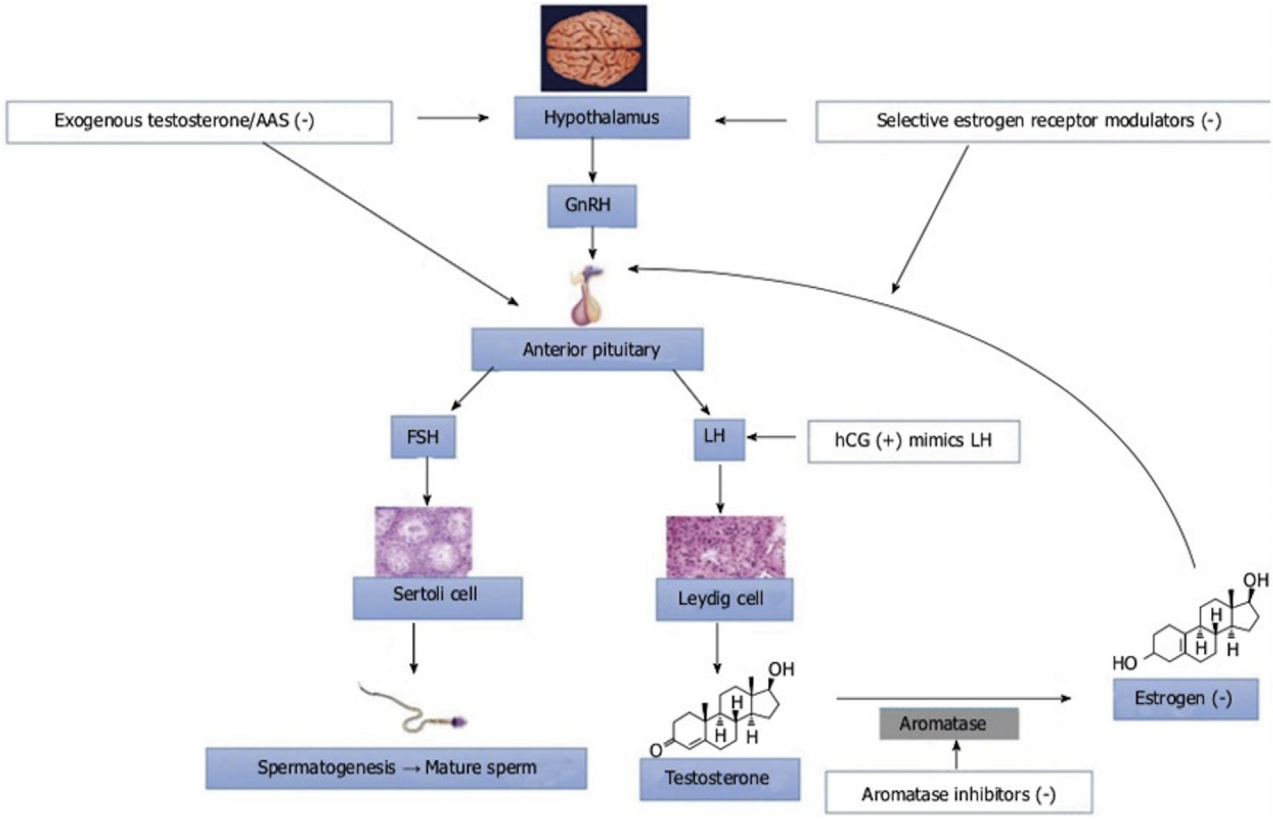

Figure 1. Hypogonadism therapeutic hormones and mechanism of action.[51] AAS = anabolic-androgenic steroid; FSH = follicle-stimulating hormone; GnRH = gonadotropin-releasing hormone; hCG = human chorionic gonadotropin; LH = luteinizing hormone. Figure 1 is available in color online at www.jsm.jsexmed.org.

(Figure 1). During CC therapy, the frequency and amplitude of gonadotropin-releasing hormone pulses increase, stimulating the pituitary gland to release more FSH and LH. Consequently, sperm and testicular testosterone productions are increased.[15,17] CC is readily absorbed orally in humans and reaches peak plasma concentrations within 6 hours. The half-life of its oral dose is approximately 5 days, but trace amounts of drug have been found for at least 6 weeks after dosing.[17] CC is metabolized by the liver and is contraindicated in patients with liver dysfunction. However, little data exist on the exact pathways involved in CC metabolism.[17] 5 days after a single oral dose, approximately 50% of CC is excreted (42% by fecal excretion and 8% by urinary excretion).[16]

Effects on Testosterone

CC is relatively effective at raising serum testosterone levels. Several studies investigated CC use in the treatment of hypogonadism (Table 1).[18–24] In 2003, Guay et al[18] evaluated the effect of a 4-month course of 50 mg oral CC 3 times weekly on 173 men with hypogonadotropic hypogonadism and ED. Free testosterone levels increased from 9.3 to 21.2 pg/mL ($P < .001$). In 2009, Taylor and Levine[19] recorded similar biochemical effects in 42 patients with a rise of testosterone from 277 ng/dL to 573 ng/dL after an average treatment duration of 23 months with 50 mg CC daily. 2 years later, Katz et al[20] examined 86 men with testosterone levels lower than 300 ng/dL. Patients received CC 25 to 50 mg every other day and attended follow-up after a mean of 19 months of therapy. TT and the testosterone/estrogen (T/E) ratio increased from a baseline of 192 to 485 ng/dL and 7.4 to 12.4, respectively. Moskovic et al[21] validated those results in their study population of 46 patients with hypogonadism, using 25 mg or 50 mg CC every other day. With a mean follow-up of more than 12 months, patients had a significant improvement in their testosterone levels and T/E ratio, from 228 ng/dL to 612 ng/dL and 6.1 to 12.8, respectively. In 2014, Ramasamy et al[22] investigated a retrospective comparison between hypogonadal men on testosterone injections, gels, CC, or no therapy. The authors found eugonadal serum testosterone levels in men on CC and testosterone gels (504 ng/dl and 412 ng/dl, respectively). Patients treated with CC demonstrated an increase in their T/E ratio, from 12.4 to 25.2. Another retrospective study of Chandrapal et al[23] recorded 77 male infertility patients with symptomatic hypogonadism, who were placed on 50 mg of CC every day or every other day. The use of CC significantly raised both mean total and bioavailable testosterone levels by 200 ng/dL and 126 ng/dL, respectively ($P < .001$). Recently, Dadhich et al[24] compared 75 men undergoing TRT vs CC in a prospective cohort study and found that both had an increase in serum testosterone after therapy

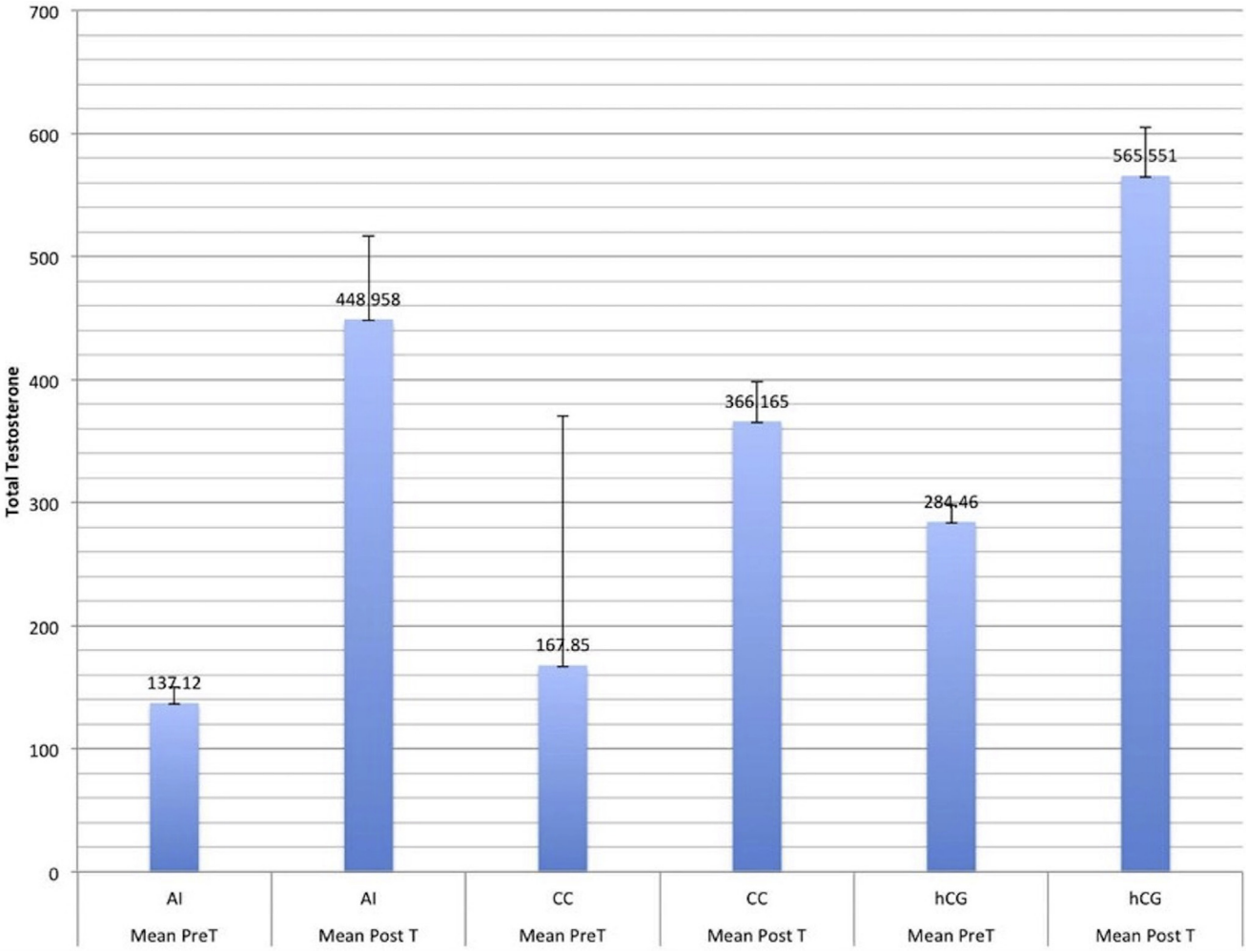

Figure 2. Mean total testosterone (TT) before treatment vs after treatment of aromatase inhibitors (AIs), clomiphene citrate (CC), and human chorionic gonadotropin (hCG). Figure 2 is available in color online at www.jsm.jsexmed.org.

(+260 ng/dl vs +203 ng/dl). The T/E ratio in the CC group improved from 11.7 to 12.5. In 2018, Soares et al[25] published a randomized, double-blinded, placebo-controlled trial evaluating the effects of CC in obesity-associated male hypogonadism. Patients received either CC or placebo for 12 weeks. Compared with the placebo group, the CC group had an increased serum testosterone level of nearly 500 ng/dl over baseline. In addition, the T/E ratio in the CC group improved from 8.2 to 21.2. Figure 2 summarizes the mean TT before treatment vs after treatment of CC.

Effect on Symptoms Associated with Hypogonadism

Testosterone-elevating effects of CC appear to benefit libido, erectile function, and sexual function reflected in the ADAM, qADAM, and IIEF questionnaires. In study by Guay et al,[18] 75% of patients had improved erectile function. Taylor and Levine[19] showed that CC effects translated into a significant decrease trend in the ADAM questionnaires' scores. By analyzing question 1 (Do you have a decrease in libido or sex drive?) and 7 (Are your erections less strong?), they found that the libido and erectile function significantly improved. Similarly, in the study by Katz et al,[20] there was an improvement in all questions on the ADAM questionnaire, with the trend of deceasing mean scores. 2 months later, Moskovic et al[21] recorded a significant improvement in the ADAM scores of their patients with hypogonadism after CC treatment. In comparison of CC with testosterone therapies by Ramasamy et al,[22] ADAM scores were significantly improved by CC to the same extent as testosterone injection and gel. Chandrapal et al[23] reported that the improvement in testosterone was translated to symptomatic improvement based on ADAM scores, but this was not reflected in the IIEF score. Similarly, overall ADAM scores decreased in the study by Dadhich et al.[24] Recently, Soares et al[25] described a reduction in hypogonadal symptomology in obese men treated with CC, as assessed by ADAM scores. Overall, these studies highlight the ability of CC to raise testosterone and ameliorate hypogonadal symptoms. This evidence suggests that there may be a larger role for CC as treatment for hypogonadism as an alternative to testosterone therapy, especially in younger men desiring fertility preservation. Table 1 summarizes the studies that detailed CC effect on testosterone and hypogonadism.

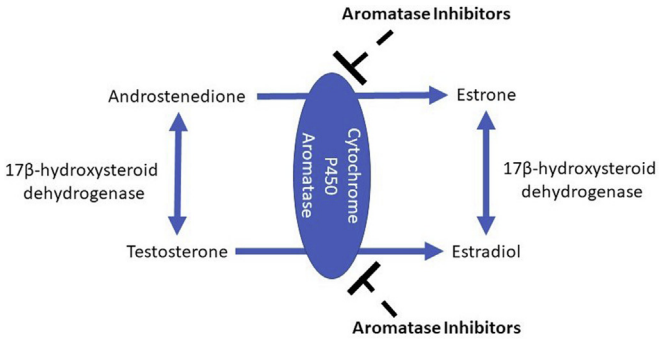

Figure 3. Cytochrome P450 aromatase effects.[52] Figure 3 is available in color online at www.jsm.jsexmed.org.

Potential Side Effects

Because all the alternative therapies mentioned in this manuscript function by indirectly increasing testosterone, effects that may be directly related to testosterone will not be discussed. CC is tolerated well by most patients. Common side effects include gastrointestinal distress, dizziness, hair loss, gynecomastia, and minimal weight gain.[17] The most common adverse events reported are hot flashes (10%) and visual disturbances (<2%). Few case reports have mentioned that some patients have encountered visual disturbances such as blurred vision, photophobia, and diplopia. Visual disturbances during CC therapy are possibly due to vascular sludging, which leads to ischemic optic neuropathy.[17] Fortunately, these effects are reversible on cessation of the medication. Other side effects associated with CC include cervical mucus abnormalities and luteal phase deficiency in women.[17] There have been few reports about CC affecting sperm parameters; however, the extent does not rival that of TRT's impact on spermatogenesis.[26,27] Finally, there has been a case report of deep vein thrombosis in a 32-year-old man whose only remarkable risk factor was clomiphene usage.[28] Finally, in one study evaluating TRT vs CC, the patients treated with CC were found to have a statistically decreased risk of developing increased hematocrit levels on a multivariant analysis.[29]

Aromatase Inhibitors

An alternative option for non-testosterone–based hormonal therapy are the AIs. Drugs within this class such as anastrozole and letrozole have been established as the standard of care for ER-positive breast cancer in postmenopausal women.[30,31] Off-label use of AIs has increased by male patients seeking alternatives to exogenous testosterone for conditions such as hypogonadism and male infertility. AI use stimulates gonadotropin release by inhibiting the synthesis of estradiol, which itself is a potent inhibitor of the HPG axis.[31] This section will review the biologic mechanism of action and relevant literature regarding the effects of AIs on testosterone and hypogonadic function.

Biopharmacology and Mechanism of Action

Cytochrome P450 aromatase is an enzyme that is present in the male brain, adipose tissue, and testis and female reproductive organs. Aromatase converts androstenedione to estrone and testosterone to estradiol (Figure 3). AIs inhibit this pathway, thereby preserving testosterone levels and limiting estrogen production. The first discovered member in this class was testolactone, which is an irreversible, non-specific steroidal inhibitor of aromatase.[32] Letrozole and anastrozole are third- and fourth-generation specific non-steroidal competitive antagonists of aromatase, respectively.[30,31]

Effects on Testosterone

The literature on anastrozole focuses largely on the drug's effects on testosterone and semen parameters. Saylam et al[33] identified 27 infertile men with total serum testosterone <330 ng/dl and T/E ratios of 10% and administered 2.5 mg letrozole orally once daily. In this cohort, testosterone levels increased from a mean of 255 ng/dl to 527 ng/dl, with a decrease in serum estrogen levels from 25.93 to 14.68. Body mass index, FSH, and LH levels remained unchanged. Leder[34] randomized 37 hypogonadal men (total serum testosterone < 350 mg/dl) with a mean age of 67 years to either anastrozole 1 mg daily, twice weekly, or placebo. They found that daily anastrozole increased testosterone from a mean of 343 ng/dl to 572 ng/dl, and twice weekly dosing increased testosterone levels from a mean of 397 ng/dl to 520 ng/dl. Both cohorts saw decreased levels of estrogen. CC and anastrozole have also been compared head-to-head by Sevann Helo and Clay Mechlin[35] in a randomized cohort of 26 hypogonadal infertile men. Testosterone levels increased significantly for both arms, but the increase was more pronounced in the CC group, whereas an increase in the T/E ratio was only significant in the anastrozole group. Letrozole vs anastrozole, when compared by Gregoriou et al,[36] appears to increase TT as well as T/E ratios equally. This profile of hormonal change characterized by increase TT, and increased T/E ratios have been demonstrated in a number of studies summarized in Table 2.

Effect on Hypogonadal Symptoms

While the hormonal impacts of AIs are well described, clearly defining the drug class's influence on sexual function such as libido, orgasm, and erectile function is a complex task, as these domains are often multifactorial. Estrogens have been demonstrated to have libido-promoting effects in hypogonadal men, whereas estrogen administration has led to decreased sexual desire and worse erectile function in eugonadal men. This is likely explained by the dependence of sexual function on a balance between the 2 hormones.[30,31] Leder's[34] study did not demonstrate any significant change in the IIEF with either twice weekly or daily anastrozole dosing. This was echoed by the work of Sevann Helo and Clay Mechlin,[35] which also did not see any change in IIEF or ADAM scores. The 2002 study by Raman and Schlegal[32] reported that 5 of 104 men treated with anastrozole complained of a decreased libido but without any validated questionnaire scoring. A 2003 single case report on a man with

intractable complex partial seizures and symptomatic hypogonadism treated with letrozole reported improved sexual function and decreased seizure activity.[37]

Potential Side Effects

Dias et al[38] randomized 43 men with a mean age of 71 years and TT levels less than 350 ng/dl to be administered testosterone gel, anastrozole 1 mg daily, or placebo. They reported men on AIs had lower lumbar spine bone mineral density than those on transdermal testosterone. 2 patients on AIs reported joint and tendon pain and swelling in their limbs. Other reported side effects in a single patient on AIs included decreased libido, irritability, depression, bilateral breast tenderness, ocular pruritus gradually turning into ocular pain, and dry mouth. Another patient demonstrated a paradoxical increase in estradiol. One patient reported transient bilateral ankle swelling, which resolved while continuing treatment.[39] In terms of cardiovascular risk, Dias et al[40] studied cardiovascular markers among patients with low testosterone. They evaluated lipid profiles, metabolic parameters, adipokines/inflammatory markers, and sex steroids among patients receiving TRT (n = 10) or AI (n = 10) treatment. At the 12-month follow-up, there was no difference in cardiovascular markers among the 2 groups.

Human Chorionic Gonadotropin

hCG was discovered in 1927 when blood and urine from pregnant women were shown to have gonad-stimulating effects on immature female mice.[41] Within 4 years, the hormone was able to be purified and made commercially available in 1931 under the brand name Pregnon, renamed to Pregnyl in 1932. The majority of currently available hCG products are still obtained from highly purified pregnant female urine, with the exception of Ovidrel that is manufactured using recombinant DNA. hCG is currently Food and Drug Administration approved for the treatment of prepubertal cryptorchidism not because of anatomic obstruction, selected cases of hypogonadotropic hypogonadism, and induction of ovulation in female infertility.[41] Within the field of andrology and infertility, hCG is used in the treatment of men with azoospermia or oligospermia resulting from exogenous TRT. This section will review the biologic mechanism of action and relevant literature regarding the effects of hCG on testosterone and hypogonadal function.

Biopharmacology and Mechanism of Action

hCG is a glycoprotein hormone made of 237 amino acids with a molecular mass of 36.7 and is composed of an alpha and beta subunit. The alpha subunit is structurally identical to that of the glycoprotein hormones thyroid-stimulating hormone, LH, and FSH. The beta subunit of hCG has a series of 121 amino acids that are identical to the biologically active 121 amino acids of the LH beta subunit responsible for interactions with the LH receptor.[41] Owing to these structural similarities, hCG is used to stimulate testosterone production by the Leydig cells while not suppressing the HPG axis.

Effects on Testosterone

The literature on the uses of hCG in men has centered on the drug's use in hypogonadal men who wish to preserve fertility. The few studies that reported effects on serum testosterone in men are listed in Table 3.[39,41–44] One of the earliest studies was carried out by Buvat et al[45] in 1987. 45 cases of psychosomatic ED (n = 39) or lack of sexual desire (n = 6) were treated in 1 month, either with hCG or with placebo using a double-blind method. This study was performed in men with physiologically normal levels of testosterone and hCG improved the serum testosterone level from a mean of 609 ng/dl to 1060 ng/dl.[39] Several years later, Tsujimura et al[42] evaluated the efficacy and safety hCG for hypogonadal patients. Twenty-one men with symptoms related to hypogonadism were included in this study. The treatment period was from 3 to 24 months. Serum concentrations of testosterone and the T/E ratio increased significantly from 210 to 270 ng/dl and from 7.3 to 9.5, respectively. Another study from Ishikawa et al[43] in 2007 included 26 patients who are hypogonadal with 25-month follow-up. The Aging Male Symptoms score significantly decreased in the hCH group with 53.6 ± 9.4 (before hCG) and 42 ± 11.0 (after hCG). In addition, the use of hCG significantly raised both the testosterone level and T/E ratio level to 400 ng/dL and 21.9, respectively. In 2015, La Vignera et al[44] evaluated 40 hypogonadal patients treated for 6 months with hCG and 3 different formulations of testosterone: transdermal, undecanoate, and enanthate. Hormonal and sperm parameters were evaluated and compared. The authors reported that testosterone levels were significantly increased in all 4 groups, whereas the Aging Male Symptoms scale remained comparable between groups. Notably, the 3 groups treated with testosterone showed a significant reduction of sperm density and percentage of spermatozoa motility compared with the hCG group. Recently, a study evaluating the use of hCG or CC in 282 hypogonadal men who wished to preserve fertility was published by Mohamad Habous and Alaa Tealab.[46] The authors found that, after 3 months of treatment, hCG, CC, and combination therapy improved serum testosterone levels by 245 ng/dl, 304 ng/dl, and 305 ng/dl, respectively. Figure 2 summarizes the mean TT before treatment vs after treatment of hCG.

Effect on Hypogonadal Symptoms

Few studies have evaluated the effect of hCG on the treatment of male sexual impairment. Buvat et al[45] suggested that hCG might be a useful option in treatment of non-organic ED and lack of sexual desire. hCG injections given twice a week clearly improved sexual behavior in nearly 50% of the cases of non-organic erectile failure or lack sexual desire. Several years later, Tsujimura et al[42] reported an improvement in the ADAM score and the IIEF score in the patients treated with hCG. In 2007, Ishikawa et al[43] showed clinically significant improvements in

the erectile function of hypogonadal men treated with hCG. Similarly, La Vignera et al[44] described improvement on ADAM and IIEF scores in their study. The ADAM score was reduced from 46 to 36, whereas the IIEF score increased from 6 to 10. Recently, Mohamad Habous and Alaa Tealab[46] reported hCG treatment improving qADAM scores. Data supporting the use of hCG in hypogonadal men are promising but less developed than that of CC and AI. In addition, recent studies have shown that hCG can stimulate recovery of spermatogenesis from TRT-induced azoospermia.[46,47] These factors make hCG a prime target for a future study. Table 3 summarizes the studies detailing hCG effect on testosterone and hypogonadism.

Potential Side Effects

The main disadvantage of hCG is frequent injections and injection side pain. Nausea, vomiting, and breast pain are all theoretical side effects that could be extrapolated from other populations, but none have been specifically reported in hypogonadal male use.[48,49]

Length of Treatment

It is important to note the duration of treatment can affect a patient's response to therapy. Several published studies have indicated short-term treatment is ineffective in addressing symptoms such as abnormal bone density. While a handful of studies included in this analysis had a treatment duration >1 year, most studies treated patients for 3–5 months. Extended treatment duration studies would be beneficial to evaluate the long-term effects on ADAM scores.[50]

CONCLUSIONS

CC, AI, and hCG have demonstrated their ability to raise testosterone while preserving spermatogenesis. This makes them prime agents to treat hypogonadism in men wanting to preserve fertility. Our results show statistically significant improvement in TT in all 3 medications after treatment. Although CC and hCG also demonstrated the ability to ameliorate hypogonadal related symptoms, there is no current evidence that AI does to a significant degree. Future studies are warranted to elucidate the relationship between improved hypogonadism and erectile function in the setting of non-testosterone–based treatment.

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