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Treatment of Male Obesity-related Secondary Hypogonadism and the Effects on Fertility

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by

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Table of Contents

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Abstract

The link between obesity and testosterone deficiency has often been a topic of research. Male obesity-related secondary hypogonadism (MOSH) is often underdiagnosed in the young male population. The current standard of care for hypogonadism in the older male population typically includes testosterone replacement therapy (TRT). The purpose of this study is to highlight available treatment options for MOSH in the younger population and the various effects on fertility. The method utilized was a systematic review of the current literature that targeted obese males below the age of 65 treated for secondary hypogonadism. The review excluded articles published longer than ten years ago or if the studies chosen solely included animals. To date, there has not been a consensus statement made for specifically treating the young male with a diagnosis of MOSH who desires the preservation of fertility. This review highlights some of the current recommendations, including lifestyle changes, and compares the use of TRT and selective estrogen receptor modulators (SERMs) and the effects on reproductive health. Promisingly, SERMs were found to be more protective of sperm production than traditional testosterone replacement. Many providers and patients need further education on this topic. Future research is needed to include randomized controlled trials (RCTs) that directly compare SERMs with TRT to provide definitive data supporting the use of this alternative treatment.

Keywords: male obesity, testosterone levels, and MOSH

Introduction

Obesity is a tremendously prevalent condition that health care professionals often encounter in the primary care setting. It can be multifactorial, complex to manage, and lead to a multitude of comorbidities. The link between obesity and testosterone deficiency has often been a topic of research. Male obesity-related secondary hypogonadism (MOSH) is a diagnosis one should consider in an obese male with evidence of clinical symptoms including but not limited to gynecomastia, impaired sexual performance, or low bone mineral density (BMD). MOSH is associated with a myriad of sequelae not limited to fatigue, lack of libido, erectile dysfunction, decreased muscle mass, decreased BMD, and fertility issues. To manage these symptoms, clinicians may explore the addition of testosterone replacement therapy (TRT). The purpose of this study is to highlight available treatment options for MOSH and the various effects on fertility.

Statement of the Problem

MOSH is often underdiagnosed and an undertreated condition in the young male population. Risk factors, such as genetics and lifestyle, contribute to obesity. Providers must also consider hypogonadism as a contributing factor for obesity or as a resulting outcome of obesity. The current standard of care for hypogonadism in the older male population typically includes TRT. Treatment options for the young male population must also consider preserving fertility if desired by the patient. Various treatment options may include diet and exercise, TRT, or selective estrogen receptor modulators (SERMs). Further research comparing alternative treatment options such as SERMs with traditional testosterone therapy and the differing effects on sperm production would benefit the primary care provider in the decision-making process.

Research Question

In a young adult male diagnosed with MOSH, is TRT or the use of SERMs more effective in preserving sperm production?

Methodology

Various health science databases were utilized for reviewing the current literature, including CINAHL, PubMed, Cochrane Library, and Embase. Keywords searched included male obesity, testosterone levels, and MOSH. The search revealed 171 articles. Articles and studies related to older men, primary hypogonadism, comorbid conditions of prostate cancer and type 2 diabetes, and studies explicitly monitoring prostate-specific antigen (PSA) levels were excluded. The review also excluded articles published longer than ten years ago or if the studies chosen solely included animals. The last search yielded 20 articles with inclusion criteria of studies performed in the US and abroad, randomized controlled trials (RCTs), peer-reviewed journal articles, and systematic reviews. Finally, 12 articles were chosen. The patient population targeted were obese males below the age of 65 treated for secondary hypogonadism.

Literature Review

A review of the current literature shows that the most prescribed treatment of MOSH is using diet and exercise with or without testosterone therapy. Current research is underway that substitutes the use of SERMs versus testosterone therapy to assist in improving levels versus replacement. The goal of SERMs is to preserve spermatogenesis while elevating testosterone levels. After further testing, this could become the preferred treatment for a young male diagnosed with MOSH that desires fertility.

Defining Male Obesity-related Secondary Hypogonadism

Obesity and testosterone deficiency are closely linked. Fernandez, Chacko, and Pappachan (2019) authored an article that discusses the condition of MOSH. It provides information that includes statistics, the pathophysiology of MOSH, clinical presentation, diagnostic approach, and treatment options. The authors utilized a comprehensive review of the literature, including extensive searches on Google Scholar, PubMed, and PMC free articles with a final of 106 articles chosen. Literature from between 2000-2019 is referenced in the text. The authors acknowledged that the review does not report any new clinical data or scientific studies performed by any of the authors themselves. The method chosen was a double-blind peer-review process. There was a narrowed topic focus, and there was no financial funding received during the article's publication. Readers may consider the article's 19-year inclusion criteria a weakness because a percentage of the information may not be current. Citations include RCTs on both humans and animals, prospective cohort studies, observational studies, systematic reviews, and meta-analysis. The article cites a statistically significant reduction in fat mass (3.5 kg, $p = .03$) using TRT in obese men. No other p values are listed other than for a study comparing liraglutide to TRT, which will not be discussed. A lack of p values, confidence intervals, and N values are limitations of this article.

Fernandez et al. (2019) included relevant statistics highlighting the prevalence of obesity in this comprehensive review. According to the World Health Organization (WHO; 2020), 39% of adults are overweight, with 13% of those categorized as obese. The authors suggest that one of the significant risk factors for low testosterone is having an obese body habitus. One theory is that MOSH results from increases in leptin, insulin, proinflammatory cytokines, and estrogen levels. Fernandez et al. (2019) found that these increases lead to "functional hypo-gonadotrophic

hypogonadism with the defect present at the level of the hypothalamic gonadotropin-releasing hormone (GnRH) neurons" (p. 83). Testosterone deficiency symptoms include visceral fat, insulin resistance, inflammation, and low sex hormone-binding globulin (SHBG) levels. Patients with MOSH generally demonstrate normal levels of luteinizing hormone (LH) and follicle-stimulating hormone (FSH), indicating a hypothalamic problem rather than at the pituitary level. It introduces the theory that adipose tissue enhances aromatase enzymes, which in turn converts androgens to estrogens. The increased estrogen levels formed cause negative feedback at the hypothalamic-pituitary level, further lowering testosterone levels (Fernandez et al., 2019).

Fernandez et al. (2019) go on to define the criteria for diagnosis. A diagnosis of MOSH is made based on the following: body mass index (BMI) >30 kg/m^2, clinical hypogonadism symptoms such as impaired sexual, physical, or mental performance, impaired sexual characteristics, gynecomastia, breast pain, sleep problems, glycemic dysfunction, flushing, low BMD, unexplained anemia, morning total testosterone (TT) levels less than lower limit for healthy young males as measured using a reliable assay confirmed twice. If abnormal SHBG is evident, free testosterone (FT) or bioavailable testosterone is less than the lower limit for healthy young males in a reliable assay. LH or FSH is low or inappropriately normal, and all other causes of hypogonadism are excluded.

Seyam, Gandhi, Joshi, Smith, and Khan (2019) found that there has been little research done regarding obesity and gonadal function. The authors intend to present alternatives to the often-prescribed TRT in obese men with hypogonadism. The methodology was an extensive search performed on MEDLINE and PubMed to review published literature on the role of aromatase in adults with MOSH. The authors emphasized data published in the last five years; however, dates were not restricted during the search. The authors did not have any set of exclusion

criteria. Keywords utilized were aromatase, hypogonadism, obesity, male erectile dysfunction, androgens, estrogen, and pituitary glands. Seyam et al. (2019) report that quality assessment includes the use of "the relative citation ratio derived from iCite bibliometrics" (p. 408). There were no conflicts of interest, and the focus was narrow, mainly limited to the role of aromatase. During the search, the authors reviewed 107 articles from the years 1995-2018. Of the citations chosen, only five were RCTs. The remaining references in the review were longitudinal studies, systematic reviews, meta-analysis, or expert opinions. A limitation found was that the authors seemed to be significantly biased against testosterone replacement therapy and made sure to emphasize its addictive quality. The total population numbers of the included RCTs were 96 (N = 96) and demonstrated heterogeneous selection. There were no CI or p values recorded.

Seyam et al. (2019) go on to write that under normal circumstances, the hypothalamus secretes GnRH, stimulating the anterior pituitary gland to release FSH and LH. Leydig cells secrete androgen and testosterone in response to stimulation by LH. In turn, 5 alpha-reductase enzyme converts testosterone, found in the adrenal glands, into dihydrotestosterone (DHT). A negative feedback loop exists between the testes and the pituitary gland. If levels of DHT or testosterone are high, the anterior pituitary gland diminishes the production of LH. Male hypogonadism occurs when there is a failure to produce enough testosterone available for physiological needs. Causes are grouped into primary or secondary. Primary hypogonadism involves damage to the seminiferous tubules. Secondary hypogonadism, or MOSH, suggests that the disease or damage has occurred at either the hypothalamus or the anterior pituitary. Results include low or normal FSH or LH and low testosterone and sperm count (Seyam et al., 2019). Laboratory testing and imaging, such as an MRI of the pituitary, are useful when distinguishing between primary and secondary causes. Labs include testosterone levels, sperm count, FSH, and LH concentration.

Serum testosterone levels should be performed between 8:00 and 10:00 am since the highest levels occur in the early morning. Obese males have an increased level of white adipose tissue, which increases aromatase activity. It is theorized that the excess aromatase function may cause low testosterone in obese males due to increased conversion of androgens into estradiol. The testosterone to estradiol shunt leads to secondary hypogonadism (Seyam et al., 2019).

An Overview of Testosterone Therapy

Bhasin et al. (2018) reported that the Endocrine Society appointed a task force to update a previously published guideline in 2010 regarding the use of testosterone therapy in men with androgen deficiency. The task force included ten participants, nine of which were medical content experts and one clinical guideline methodologist. The methodology for developing the guidelines consisted of two systematic reviews and utilized the best evidence available from other reviews and studies. The consensus involved using the grading of recommendations to describe the recommendations' strength and the quality of the evidence presented. A total of 156 references were included in the review and varied from journal articles to RCTs. The committee members appointed were supported by the Endocrine Society and received no other financial support. None of the ten participants declared any financial disclosures. Only one declared an uncompensated leadership position in the American Society for Bone and Mineral Research and Partnership for the Accurate Testing of Hormones. Cosponsoring organizations were the European Society of Endocrinology with an endorsement made by the European Academy of Andrology.

Bhasin et al. (2018) note that the task force followed the approach laid out "by the Grading of Recommendations, Assessment, Development, and Evaluation Group, an international committee with expertise in the development and implementation of evidence-based guidelines" (p. 1717). The quality of evidence and the strength of recommendations use consistent language.

Several statements underscore the importance of informing the patient of testosterone therapy's risks and benefits and allowing shared decision-making, general preventative care measures, and diagnosis and treatment principles. The Endocrine Society has rigorous conflict-of-interest rules. All members must declare any potential conflicts by completing a form and undergoing a subcommittee review before approval and periodically throughout the guideline development process. Of the two systematic reviews performed by the task force, the first one determined if TRT improves sexual and physical function, mood, cognitive status, anemia, BMD, and fatigue in men with clinical hypogonadism. The second review will be briefly mentioned. The trials included were placebo-controlled with subjects having a TT level of less than 300 ng/dL and whose levels were raised by the treatment into a normal range. The study only uses testosterone or esters for therapy. This review consisted of 11 different reports of four trials, with 1779 participants (N=1779) ranging from 12 to 52 weeks. The trials used either allocation-by-minimization or randomization and featured a low bias risk. Statistically significant results were improvement in libido (95% CI [0.01, 0.34]), sexual activity (CI [0.13, 0.33]), sexual satisfaction (CI [0.01, 0.31]), and erectile function (CI [0.06, 0.27]). The second review looked at whether TRT has linkage to an increased risk of lower urinary tract symptoms (LUTS) and erythrocytosis in men with clinical hypogonadism. This review consisted of nine studies of three trials, with 1581 participants (N=1581) ranging from 12 to 52 weeks. Results were a higher frequency of hematocrit >54% (RR of 8.14; 95% CI [1.87, 35.40]). There was no statistical difference in the incidence of LUTS.

The authors present a consensus guideline for using testosterone therapy that lists the most common benefits and adverse effects. Highlights worth mentioning include a Grade 1 recommendation against routine screening for hypogonadism within the general population and a Grade 1 recommendation to use TRT in hypogonadal men to induce and maintain secondary sex

characteristics and correct symptoms. A Grade 1 recommendation is presented against TRT in men planning fertility soon. The recommendation also includes not using TRT in men with breast or prostate cancer, a PSA greater than 4ng/mL, elevated hematocrit, untreated severe OSA, severe LUTS, uncontrolled heart failure (HF), MI, thrombophilia, or CVA within the last six months. Benefits found with testosterone therapy that were listed include the induction of secondary sexual characteristics, improved libido, erectile function, and sexual activity versus placebo, increase in volumetric vertebral and femoral BMD, and fat reduction. Adverse effects included acne, oily skin, breast tenderness, erythrocytosis, decreased HDL, and spermatogenesis suppression.

Owen, Elkelany, and Kim (2015) conducted a literature review with 36 cited references dated from 1995 to 2014. The authors sought to educate the obstetrician/gynecologist on recognizing an iatrogenic induced form of decreased sperm production in couples seeking fertility advice. Two of the three authors had no disclosures. The article intends to provide a consensus of the literature to assist the medical professional in treatment decision-making. A limitation is that the article is a literature review instead of a RCT. Furthermore, the information spans 19 years; however, recent updates are provided. No CI or *p* values are included in the review. It is worth mentioning that the third author is an advisor for a reproductive therapeutic company and a speaker for a pharmaceutical company; nevertheless, this author received no financial assistance.

Owen et al. (2015) found that hypogonadal men may experience decreased libido, low energy, decreased erections, small testes, infertility, low concentration, sleep problems, and reduced muscle mass. The article highlights current practices involving TRT. "From 2010 to 2013, the number of testosterone prescriptions increased from 1.3 million to 2.3 million patients" (Owen et al., 2015, p. 259). The increase in the use of testosterone therapy in men of reproductive age may have a negative effect on fertility. Additionally, the treatment route is essential in that topical

testosterone therapy may have the risk of being transferred to a female partner. Current FDA approved routes are IM injection, nasal gel, topical gel, transdermal patch, subcutaneous pellet, or buccal bioadhesive tablets. Each formulation has its various advantages and disadvantages. Adverse effects may include increased PSA, acne, fatigue, aggression, insomnia, polycythemia, deep vein thrombosis (DVT), hepatic effects, edema, gynecomastia, obstructive sleep apnea (OSA) worsening, changes in lipids, or hypercalcemia (Owen et al., 2015).

The authors further report that in 2015, the FDA directed all testosterone manufacturers to include a warning of the possible increase in stroke incidence and cardiovascular events. TRT can also result in a decline in spermatogenesis. Exogenous testosterone creates a negative feedback loop on LH, FSH, and GnRH. This feedback decreases the stimulation of Leydig and Sertoli cell functions, which slows the progression of spermatogenesis and results in a decrease in intratesticular testosterone production. The premise of the review predicates on the notion that maintaining spermatogenesis will improve fertility chances.

Non-pharmaceutical Approaches to Treatment of MOSH

A pilot study by DeLorenzo et al. (2018) evaluated the effects of diet and exercise on patients with a diagnosis of MOSH. The patients' hormonal, lipid, and glycemic profiles were measured at baseline and after a 10% weight loss. The evaluators' limited the study to include only 14 Caucasian males. Only 12 of the 14 patients completed the study, as two did not reach the required 10% weight loss. There were no conflicts of interest declared by the authors. The article published in the journal, *Nutrients*, pointed out the association between obesity and low testosterone and the implications on the quality of life. During the study, food addiction and signs and symptoms of hypogonadism were assessed through the Yale Food Addiction Scale (YFAS) and the Aging Male Symptoms Scale (AMS), respectively. Initially, 20 patients from January 2016

to September 2016 were screened in Rome, Italy. The study took place at two centers. Participants, who were age 18-65, were excluded if they had comorbidities of major psychiatric disease, cancer, infections, or autoimmune diseases. All patients received a custom dietary plan and personalized nutritional counseling with a hypocaloric, high-protein diet, and no alcohol consumption. The Mediterranean Diet was utilized and included three meals, two snacks, and probiotics daily. This diet relies on fresh fruits, vegetables, extra virgin olive oil, legumes, cereal, and fish. Each subject was encouraged to perform 150 minutes of aerobic activity per week at 50-70% of maximum heart rate with a personal trainer included as part of the team. The mean observational time in the program was 3 +/- 1 month to achieve the 10% weight loss. Overall findings included a significant increase of TT (408.3 +/- 125.9 ng/dL) as compared to baseline levels (300.2 +/- 79.5 ng/dL) with a *p* value of .002 and a 95% CI [26.8, 167.7]. A reduction in 17-beta estradiol level was also observed with 48.3 +/- 14.9 pg/mL at baseline versus 39.2 +/- 15.2 pg/mL upon completion with a *p* value of .049 and CI [31, 0.0].

A randomized controlled trial by Rosety et al. (2017) consisted of 90 obese adults ($N = 90$). Subjects were assigned to either the intervention group (n=45) or a control group (n=45). In the intervention group, participants completed a 16-week treadmill training program. Sessions were three times per week and involved 10-15 minutes of warm-up, 35-50 minutes of treadmill activity that increased by 5 minutes every 4 weeks at an intensity of 50-65% of peak heart rate ending with a cooldown of 5-10 minutes. Laboratory assessments included semen quality, serum levels of FSH, LH, testosterone levels, and estradiol levels. Body composition and level of fitness were also measured. Upon program completion, sperm count, sperm motility, and normal morphology were improved, and serum testosterone levels were notably increased. Subjects excluded included those participating in a prior training program in the last 6 months, testicular varicocele or genital

infection, leukocytospermia, chronic illness, vasectomy reversal, and varicocele removal, receiving medications that interfere with redox, smoker, or heavy drinker. Participants wore a wireless heart rate monitor during the aerobic training. The trial's purpose was to determine the effect of aerobic training on both semen quality and reproductive hormones in obese adult males.

A limitation of the study was the program's short duration with a lack of follow-up to determine if the short-term aerobic training had any long-term effects on the hormonal profile. The sample size was also small. The study's strengths included adherence rate to the program, concealed method for randomization of the participant's placement, and objective measurements for outcomes versus subjective or self-reporting. There were no significant changes in any of the parameters for the control group. The intervention group had an increase in LH from 4.46 to 4.58 *(p* value of .094) and increased FSH from 5.53 to 5.57 *(p* value of .166). Further findings included testosterone elevation from 4.36 ng/ml to 4.78 ng/ml with a *p* value of .036 and estradiol decrease from 56.3 pg/ml to 54.9 pg/ml with a *p* value of .220. Sperm concentration increased from 45.0 to 48.8 *(p* value of .040), and progressive motility improved from 42.6 to 46.2 *(p* value of .015).

Testosterone Replacement vs. Selective Estrogen Receptors Modulators

Alder, Keihani, Stoddard, Myers, and Hotaling (2018) compiled a study that identified a total of 51 men ($N = 51$) that were treated with a combination of clomiphene citrate (CC) and anastrozole (AZ) between the years of 2014 and 2017. The mean age was 35.4 +/- 7.4 years, and the mean BMI was 35.0 +/- 8.0 kg/m^2. Inclusion criteria were a TT level < 300 ng/dL or a bioavailable testosterone level < 155 ng/dL, along with hypogonadal symptoms or inability to conceive a child after one year in the absence of a known female factor with a partner. Baseline information gathered included BMI, medical history, Sexual Health Inventory for Men (SHIM), and Androgen Deficiency in Aging Male (ADAM) questionnaire scores. Patients excluded

included the following: any known sex chromosome disorder, recent exogenous testosterone therapy, and lack of follow-up after starting combination therapy. Baseline labs included LH, FSH, SHBG, albumin, TT, bioavailable testosterone, estradiol, and testosterone to estradiol ratio. Data collected throughout included morning TT, bioavailable testosterone, estradiol levels, testosterone to estradiol ratio. These levels were measured after treatment with CC only and after combination therapy of CC with AZ. Follow-up testing occurred after 3-4 weeks to assess treatment response. Side effects tracked included PSA and hematocrit levels after 6 months of use and any adverse reactions. Semen characteristics were also compared at baseline and after three months of combination therapy if available for analysis. "Data were analyzed using a paired t-test and Wilcoxon's signed-rank test" (Alder et al., 2018, p. 688). A paired t-test is when the researcher looks at the difference between two variables for the same subject, in this case, with and without combination therapy.

Alder et al. (2018) separated the men into two categories. Those treated with combination therapy for less than 6 months (CC + AZ, follow-up group 1) and more prolonged than 6 months (CC + AZ, follow-up group 2). The CC treatment results included an increase in TT from a mean of 257.6 to 667.2 with a p value < .001 and in bioavailable testosterone from a mean of 147.3 to 386.8 with a p value of < .001. Only 38 men had semen analysis available at baseline due to azoospermia and oligozoospermia; therefore, this data will not be discussed. Follow-up group 1 treated with CC + AZ for a mean of 9.2 weeks improved from TT baseline of 257.6 to 689.8 with a p value of .25 and bioavailable testosterone from 147.3 to 402.0 with a p value of .24. The most significant difference between the CC therapy and the combination therapy was in estradiol levels, as was anticipated since anastrozole is an aromatase inhibitor and would lower testosterone conversion to estradiol. With CC alone, the estradiol increased from 21.0 pg/mL at baseline to 65.6

with a *p* value of .001. With combination therapy, the estradiol levels were 33.9, with a *p* value of .001. Follow-up group 2 had similar findings after mean combination therapy of 32.4 weeks. A total of 11 patients or 21.5% had side effects on combination therapy that included anxiety, decreased libido, and elevated hematocrit. Four patients discontinued treatment altogether. Three patients had PSA values > 1.78 ng/mL during the treatment; however, one of these had a history of BPH and a baseline of 6.6 ng/mL that did not increase while on the medication.

This review's limitations include the fact that this is a retrospective study looking at chart reviews from a single fertility clinic between the stated period. There was no placebo control group or randomization, as would be found in a randomized controlled trial. Other weaknesses include small sample size, difficulty obtaining data on semen samples, and the possibility of selection bias. The authors acknowledge that this is the first study on outcomes and safety of combination therapy that includes CC and AZ in this patient population. Strengths include no declared conflicts of interest, data collected over 3 years, and the ability to use each patient as his control based on the availability of baseline data and follow-ups.

Giagulli et al. (2020) authored a systematic review article that looked at whether SERMs or selective androgen receptor modulators (SARMs) were useful alternatives for treating adult males with hypogonadism. The focus was on treating functional hypogonadotropic hypogonadism (HH) caused by obesity or chronic inflammatory diseases. A total of 66 references are included in the review dated between 1988 and 2019. The review cited concerns about the benefits versus risks of using TRT in younger males who wished to maintain their fertility. It proposed using SERMs, which were found to enhance the serum levels of LH and FSH due to the blocking of estrogen receptors. Common side effects reported most often were hot flashes, insomnia, and weight gain using aromatase inhibitors (AIs) and gynecomastia,

headaches, and dizziness with the use of CC. Both drug classes (SERMs and AIs) have proven to reactivate the hypothalamic-pituitary-testis axis in all conditions of hypogonadism that do not result from an organic cause. The use of SARMs was also presented; however, this information will not be discussed. There were no statistically significant values given in the authors' literature review.

This review's limitations include the rather significant period included in the search dating back to as early as 1988, which may not represent currently updated research. Another limitation is that the review focused more on mentioning the ongoing clinical trials rather than presenting published research. A strength was that the authors declared no conflicts of interest. The article confirmed TRT risks in men who wish to preserve fertility. The ability of SERMs to raise LH and FSH, which correlates positively with spermatogenesis, was highlighted throughout the review (Giagulli et al., 2020).

Kim, McCullough, and Kaminetsky (2016) compared the effects of a daily dose of enclomiphene citrate, a SERM, to topical testosterone gel regarding TT, LH, FSH, and sperm counts in men with MOSH. Two double-blind RCTs were utilized with two different doses of enclomiphene citrate versus testosterone gel. One important thing to note is that this trial is now in phase III, indicating that the study's first two phases were promising. Phase III trials are conducted to expand on the previous trials' efficacy and safety and to meet regulatory requirements. Inclusion criteria included early morning TT levels <300 ng/dL measured on two separate occasions and low or inappropriately normal LH level (<9.4 IU/L). Semen samples were provided twice at the beginning and twice at the end of the study.

The trials by Kim et al. (2016) included 256 men ($N = 256$) who received active dosing in one of the study's four arms for up to 16 weeks. A significant steady-state of TT value of > 400

ng/dL appeared after 4 weeks of enclomiphene citrate, but a steady-state was not achieved after 4 weeks of treatment with the testosterone gel. The TT levels remained low throughout the study in the placebo group. After stopping treatment, the TT did not revert to baseline in the enclomiphene groups but stayed higher than baseline ($p < .001$, Wilcoxon rank-sum test) for at least 7 days. In the testosterone group, the TT decreased quickly with values going below baseline after stopping treatment ($p = .07$, Wilcoxon rank-sum test). LH values increased for the pooled enclomiphene citrate group ($p < .001$, Wilcoxon rank-sum test) and decreased for the testosterone gel group ($p < .001$, Wilcoxon rank-sum test). There were no changes in the placebo group within the first 2 weeks. The mean LH values were > 6 IU/L after 4 weeks of treatment with the enclomiphene. There were no baseline changes to the end of the study for the placebo group ($p = .98$, *t*-test). The testosterone gel treatment group had a decrease in LH compared to the beginning of the study ($p < .001$, paired *t*-test). After the end of the study and treatment ceased, the mean LH for the men in the enclomiphene citrate group was higher than that for men in the placebo or testosterone group. Furthermore, there were similar occurrences with FSH levels. There was no statistical increase in sperm counts in any of the groups; however, there was a decrease from baseline in the testosterone gel group ($p < .001$, Wilcoxon rank-sum test). Treatment is considered successful if men achieved sperm concentrations > 10×10^6 with TT in the range of 300-1040 ng/dL. The enclomiphene arm succession rate was 63.5%. The testosterone gel arm succession was 24.7%, and the placebo arm succession rate was 5.8% ($p < .001$, Fisher's exact test).

During the studies, adverse effects (AE) were reported by 53 men, none of which were severe (Kim et al. 2016). No AEs were found more frequently in any of the groups. Two men discontinued the study due to high hematocrit, one due to high PSA, and eight dropped-out for

unreported reasons. There was one death in the 12.5 mg enclomiphene citrate group after 34 days of treatment due to an ischemic stroke, which was concluded to be related to his past medical history and a high number of risk factors. The study's conclusions and the two prior studies point to testosterone gel suppressing pituitary function and spermatogenesis while enclomiphene citrate, a SERM, stimulates LH, FH, and maintains sperm production. Based on these trials, an ideal patient for SERM would be a male with MOSH who desires to maintain his potential to father a child. The 12.5 mg dose of enclomiphene citrate showed higher TT levels as compared to the 25 mg dose.

Limitations include the fact that the authors did not include patient-reported outcomes in this study as compared to other studies. Another limitation is that the objective measures of TT levels and spermatogenesis were used, but this is not an accurate measure of fertility without actual pregnancy or live birth data. Two of the three authors disclosed that they are consultants to Repros Therapeutics, with the third author having nothing to disclose. A final limitation is the relatively shortened study duration compared to the average length of therapy in clinical practice. Strengths included the study's method: a double-blind, placebo-controlled phase III trial that is multicentered, has a relatively large sample size, a narrowed focus, and identifiable outcomes.

Rambhatla, Mills, and Rajfer (2016) suggest that men who have low serum testosterone to estradiol ratio may benefit from the use of SERMs and AIs to reverse the imbalance and make improvements on any associated lack of fertility. The systematic review included a total of 51 references, dated from 1960 to 2015. No conflicts of interest are made available to the reader. An American Urological Association survey in 2010 revealed that 25% of practicing urologists administered testosterone to infertile men to treat their infertility (Ko, Siddiqi, Brannigan, & Sabanegh, 2012). Rambhatla et al. (2016) highlight that most of these prescribers are unaware of

the inhibitory effects of exogenous testosterone on spermatogenesis due to FSH and LH secretion inhibition. Listed alternatives include clomiphene citrate (CC) and tamoxifen. A large prospective trial of 125 men ($N = 125$) that the authors cited showed a statistically significant improvement in testosterone levels from 309 to 642 ng/dL after 3 months of use of CC (Rambhatla et al., 2016). No p values or CI were given. The article's limitations are that it reviews a disease state and does not include original research.

Scovell and Khera (2018) published a review that discusses the risks and benefits of treatment for young patients with hypogonadism that desires fertility in the future. It again points out that the hypothalamic-pituitary-gonadal axis is suppressed by testosterone and warns that prolonged testosterone use may result in permanent infertility. Alternatives explored include clomiphene citrate and human chorionic gonadotropin (hCG). The systematic review consists of 19 references dated from 1997 to 2018. Two of these same studies referenced have been included in this scholarly project. The statistics show that in 2013, TRT prescriptions nearly doubled from 1.2 million to 2.2 million, with 12.4 % of these patients being under 39 years old (Nguyen et al., 2015). It addresses the need for informed and shared decision making between the patient and the provider. The population focused on men less than 35 years old who presented to the urologist with hypogonadal symptoms and a testosterone level around 270 or less on two separate morning lab draws. The AUA guidelines support the use of AIs, hCG, and SERMs for these patients. "The 2015 International Consultation for Sexual Medicine guidelines advise against using exogenous testosterone in men who wish to preserve fertility and support the use of alternative therapies similar to the AUA recommendations" (Scovell & Khera, 2018, p.322). Limitations include a relatively small number of references as compared to other systematic reviews. Another weakness could be author bias due to having only two authors, one of whom

disclosed that he is a consultant for multiple companies. No one shared any financial disclosures or specific funding. The research was supported by the National Institute of General Medical Sciences of the National Institutes of Health.

A randomized, double-blind, placebo-controlled study was presented by Soares et al. (2018). The study was performed at a single center and consisted of 78 men ($N = 78$) aged 36.5 +/- 7.8 years with a BMI > 30 kg/m^2. Participants also had a TT of less than 300 ng/dL and subjective symptoms. The study's length was 12 weeks, with subjects randomly allocated to either the treatment group of 50 mg CC or the placebo group by a computer-generated sequence. TT levels were screened twice at least 1 week apart, LH range was 1.7 to 8.6 IU/L, and participants completed the ADAM questionnaire before entry into the program. Exclusion criteria included the presence of serious chronic diseases such as liver disease, heart failure, or renal insufficiency, the practice of strenuous exercise, use of opioids, methadone, steroids, or other addictive drugs, the presence of eating disorders, prostate cancer, testicular volume below 4 mL, hyperprolactinemia, hemochromatosis, and history of smoking (Soares et al., 2018). The active group received a 50 mg/d dose for 12 weeks. Outcomes measured included responses on the ADAM questionnaire, TT, free testosterone (FT), estradiol, LH, FSH, SHBG levels, waist circumference and BMI, metabolic parameters, and endothelial function. The safety profile evaluated included hematocrit, PSA, International Prostate Symptom Score (IPSS), ALT, AST, and AE reported by the subjects. Two hundred fifty-two male volunteers were screened between June 2013 and August 2016. From this original sample, 78 well-matched men were selected.

Soares et al. (2018) state that five subjects dropped out of the CC group sometime after randomization. Six subjects dropped out of the placebo group, with three from each group considered for statistical analysis using the last observation carried forward (LOCF) approach.

Hormonal levels significantly increased in the CC group at week four and remained high during the 12 weeks ($p < .0001$). There was no change in hormonal levels in the placebo group. One participant in the intervention group discontinued the intervention because of a severe headache, and another died from pneumonia. There were no withdrawals in the CC group due to adverse effects. PSA did increase in the CC group from 0.62 +/- 0.41 ng/mL to 0.76 +/- 0.48 at end of study ($p = .023$). Self-reported events included weight gain, asthenia, drowsiness, insomnia, irritability, bowel changes, anxiety, increased appetite, urethral candidiasis, headache, perceived reduction of testes, snoring, and cramps. These were similar in both groups (Soares et al., 2018).

The study's limitations included a lack of graded information upon follow-up with the ADAM questionnaire, short-intervention time, drop-outs, and unstandardized diet and physical activity. The study also could have had an arm that included TRT for a better comparison. Strengths include that the study was a RCT approved by the local Research Ethics Committee. The authors disclosed no conflicts of interest. The authors concluded that CC treatment for MOSH has an excellent safety profile and effectively elevates testosterone levels into the normal range.

Discussion

To date, there has not been a consensus statement made available for specifically treating the young male with a diagnosis of MOSH who desires the preservation of fertility. In addition, treatment practices and recommendations vary widely across disciplines. As discussed in an article by Rambhatla et al. (2016), 25% of practicing urologists administered testosterone to infertile men to treat their infertility. A guideline presented by the Endocrine Society in an article by Bhasin et al. (2018) includes a Grade 1 recommendation against TRT in men planning fertility soon. In an article by Owen et al. (2015) in *Current Opinion in Obstetrics and*

Gynecology, the increased number of testosterone prescriptions being dispensed is highlighted while also pointing out that this increased use of testosterone therapy in men of reproductive age may have a negative effect on fertility. No alternative therapies were given in the article by Owen et al. (2015); however, Rambhatla et al. (2016) listed clomiphene citrate and tamoxifen as options. Bhasin et al. (2018) presented the benefits and risks of TRT but did not include other treatment options. A recent literature review reveals that one treatment option prescribed for MOSH is using diet and exercise and may not include testosterone therapy. As expected, it is easy to point out the problem with TRT in this patient population; however, a concrete and viable solution has not yet been established.

As stated above, conservative therapy, such as lifestyle changes, is often the first option for the hypogonadal symptoms related to obesity due to the lack of harmful side effects. A pilot study by DeLorenzo et al. (2018) was used to evaluate the effects of diet and exercise on patients diagnosed with MOSH with hormonal, lipid, and glycemic profiles measured at baseline and after a 10% weight loss. Overall findings included a significant increase of TT and a reduction in 17-beta estradiol levels after utilizing the Mediterranean Diet and 150 minutes of weekly aerobic activity. A RCT by Rosety et al. (2017) showed similar results to weekly aerobic exercise training that included mild increases in LH, FSH, and testosterone, as well as a decrease in estradiol. Of note, the participants' semen quality was also evaluated in the Rosety et al. (2017) trial and demonstrated an increase in both the concentration of sperm and progressive motility. Although both studies are limited in sample size and duration, the positive results obtained without pharmaceuticals are worth mentioning and highlight the need for further RCTs on larger sample sizes regarding these approaches to MOSH treatment.

Going a step further, some patients do not respond to conservative therapy alone. Is it correct to assume that testosterone replacement therapy is the next best option? A systematic review by Giagulli et al. (2020) focused on treating functional hypogonadotropic hypogonadism (HH) that was caused by obesity or chronic inflammatory diseases. The consensus of the references included in the review cited concerns about using TRT in younger males who desire fertility. The authors propose using SERMs, which were found to raise testosterone levels and enhance LH and FSH serum levels, which correlates positively with spermatogenesis.

Similarly, Alder et al. (2018) demonstrated safety and efficacy in the use of a SERM as an alternative treatment for MOSH in a homogenous patient population (mean age 35.4 and mean BMI 35.0) of sub-fertile men. Baseline data are presented as well as the response to treatment with CC alone and after the combined therapy of anastrozole (AZ), an aromatase inhibitor. Although this was a retrospective study and not a comparison between TRT and a SERM, it is essential to note findings of measurable increases in testosterone, LH, and FSH with the use of CC alone and with the addition of AZ. It is also worth noting the Alder et al. (2018) study may have the possibility of selection bias since this was a study from a single fertility clinic during a three-year period.

Scovell and Khera (2018) also published a review that discusses the risks and benefits of treatment for young patients with secondary hypogonadism that desire future fertility. It warns that prolonged testosterone use may result in permanent infertility. The review is a compilation of many different references that address various sides of the issue, including the caution that estrogen plays a part in many physiologic functions in men, including bone and cardiovascular health. These subjects should be monitored if receiving long-term therapy of SERMs. It acknowledges that the data supporting the use of these alternatives is under development and that

more RCTs are needed. Evidence is compiled that supports the idea that TRT affects spermatogenesis by decreasing intratesticular testosterone and FSH due to the axis's suppression. It also establishes that many providers and patients need further education on this topic.

A RCT by Soares et al. (2018) also demonstrated improvement in hormonal levels of TT, LH, and FSH with the use of CC with no withdrawals from the study due to adverse effects. The sample chosen may have been convenient as the study was performed at a single center and consisted of only 78 men. Although there was a placebo group as a control, there was no arm of comparison to TRT. Of the studies chosen in this literature review, one stood out for its impressive data. Kim et al. (2016) conducted two double-blind RCTs that are now in phase III trials, which compared a SERM to topical testosterone gel. The success rate was higher in the enclomiphene arm than in the testosterone gel arm, which accounted for both steady-state levels of TT during treatment and levels that were maintained after stopping treatment. LH values were also higher for men in the SERM group, and sperm counts decreased in the testosterone gel group while remaining the same in the SERM group. An unexpected death occurred in the 12.5 mg enclomiphene citrate arm of the study after 34 days of treatment due to an ischemic stroke; however, it was concluded to be related to the gentlemen's medical history and multiple risk factors and not from the trial itself.

Conclusion

Evidence-based guidelines demonstrate that both pharmacological and non-pharmacological approaches can treat MOSH in the young male population. Current researchers are exploring various pharmaceutical options and how these drugs affect reproductive health. As expected, this review supported the hypothesis that treatment with the use of SERMs is more protective of sperm production than traditional testosterone replacement. This treatment regimen

would be more applicable for patients who desire to preserve fertility while improving hypogonadal symptoms. Highlighted throughout this review is the awareness that many providers and patients need further education on this topic.

Future research is needed with an emphasis placed on RCTs that directly compare SERMs with TRT to provide data supporting the use of this alternative treatment. It is important to note that most of these reviewed studies looked at variables that included hormonal profile and semen quality. We must be careful not to conclude that improvement in these values will equate to an improvement in fertility. Additional studies must be designed that consider the number of partner pregnancies and actual live births that occur during or after treatment with either TRT or SERMs.

Applicability to Clinical Practice

The diagnosis and treatment of MOSH present a dilemma to clinicians today. One must be knowledgeable regarding the risks, benefits, and possible alternatives for the treatment of MOSH while also considering how reproductive health may be affected. This review aims to determine a recommendation within the primary care setting for the most efficacious treatment modality that also considers the effect on fertility for this patient population. With the information obtained, both clinicians and patients will make informed decisions while engaging in the shared decision-making process. The recent compilation of data suggests that the use of SERMs for this condition appears promising. It is crucial to note that the research in the role of SERMs in the treatment of MOSH is still ongoing and that more RCTs are needed.

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