5-2021

The Efficacy of Testosterone Replacement vs Aromatase Inhibitors/ SERMs in the Presence of Hypogonadism

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A Scholarly Project

Submitted to the Graduate Faculty of the University of North Dakota

in partial fulfillment of the requirements for the degree of

Master of Physician Assistant Studies

Grand Forks, North Dakota

May 2021

Table of Contents

Acknowledgments

First and foremost, I would like to thank my wife, Monica, for sharing in my dreams and adventures and for her love, encouragement, and wisdom. I would also like to thank Traci Leitheiser for all of her insights, edits, and input that made this project possible. Finally, I would like to acknowledge my parents Patricia and Robert Steen, without whom I would not have succeeded in my quest to provide a better life for my patients as well as my family.

Abstract

The prevalence of male hypogonadism increases with age, although it can occur in any age group. Patients with hypogonadism can experience a wide range of symptoms including mood changes, decreased libido, decreased muscle mass, erectile dysfunction and bone loss. Traditionally, management of this condition has been accomplished through some form of testosterone replacement therapy (TRT). While TRT has proven effective at attenuating the symptoms of hypogonadism, it is not without side effects. TRT can at times be expensive, painful, cause gynecomastia, acne, water weight gain and infertility. Recently, medications such as selective estrogen receptor modulators (SERMs) and aromatase inhibitors (AIs) have gained favor as alternative treatments in the presence of secondary hypogonadism. With the addition of these medications, it remains to be seen which of these three forms of treatment is the most efficacious at managing patient symptoms. After a thorough literature review which included searches of Clinical Key, Dynamed Plus, Cochrane Library, PubMed and CINAHL databases, multiple studies were reviewed to determine the effectiveness of the aforementioned treatment modalities. The results of the review discovered that TRT and SERMs are both efficacious at raising testosterone levels, improving libido, lean muscle mass, strength and endurance. SERMs appear to have one advantage over TRT in that they preserve male fertility. The efficacy of the coadministration of AIs and TRT was also examined, however, at the present there is not enough research to determine the efficacy of this treatment. With the addition of off-label therapies such as SERMs, providers will be able to customize a treatment plan for their patients that will provide a continuous steady level of testosterone all the while preserving fertility with the same benefits of TRT.

Introduction

According to Sizar & Schwartz (2020), hypogonadism in men is a reduction in the circulating hormone testosterone (<300 ng/dL), which is produced predominantly by the Leydig cells in the testes. Men with hypogonadism often report having decreased libido, fatigue, loss of muscle mass, sleep disturbances and depression. There are two forms of hypogonadism; first, primary hypogonadism results from testicular failure whereas secondary hypogonadism is attributed to hypothalamic or pituitary dysfunction. Treatment of both forms of hypogonadism is often accomplished by some form of testosterone replacement therapy (TRT). Recently, off label uses of selective estrogen receptor modulators (SERM)s and aromatase inhibitors (AI)s have been gaining favor as an off-label therapy for secondary hypogonadism. AIs work by blocking the enzyme aromatase which converts testosterone into estrogen (Mechlin et al, 2014). Estrogen is responsible for closing the negative feedback loop associated with testosterone production by inhibiting gonadotropin-releasing-hormone (GnRH and reducing GnRH sensitivity of the pituitary (Pitteloud,2008). Therefore, by reducing the conversion of testosterone to estrogen, the feedback loop remains open and GnRH stimulates further luteinizing hormone (LH) production, which in turn increases production of testosterone by the testes. SERMs act by blocking estrogen receptors in the body which in turn block the estrogen negative feedback loop and allow for the continued production of LH, follicle-stimulating hormone (FSH), and subsequently testosterone (Wiehle et al,2014). The purpose of this study is to determine whether testosterone replacement therapy, SERMS or the coadministration of TRT and AIs are more effective at managing hypogonadism.

Statement of the Problem

TRT, SERMs and AIs have shown efficacy with replacing or increasing testosterone in men; however, each form of therapy is not without risk. TRT has been associated with an increased risk of polycythemia, infertility, stroke, TIA, increased estrogen and myocardial infarction, whereas AIs/SERMs have been associated with muscle and joint pain and the possibility of bone loss. In addition to the risks associated with these treatments, it remains to be determined which of the therapies are more effective at raising testosterone levels and reducing patient symptoms.

Research Question

In men with secondary hypogonadism, is TRT, SERMs, or the coadministration of TRT and AIs more efficacious at attenuating the symptoms of hypogonadism?

Methods

An extensive literature review was conducted to combine the results of multiple studies that have evaluated the efficacy of TRT, and SERMs as well as studies that have examined the coadministration of AIs and TRT, and their use in hypogonadism. A literature review utilizing electronic academic search databases included, Clinical Key, Dynamed Plus, Cochrane Library, PubMed and CINAHL to research both forms of management for hypogonadism. Keyword and MeSH terms were used to narrow search results. The MeSH terms included selective estrogen modulators and hypogonadism with 249 results; testosterone replacement therapy, hypogonadism, and efficacy with 190 results; and aromatase inhibitors and testosterone replacement therapy with 41 studies. During the review of the SERM search, 184 articles were excluded as they were greater than 10 years old, an additional 58 studies that were not randomized control trials (RCT) or metanalyses were also excluded. Of the remaining 7 results, 2

were chosen for their relevancy of raising testosterone levels and treatment of symptoms. In the testosterone replacement therapy, hypogonadism, and efficacy with 190 results, 75 were greater than 10 years old and were therefore excluded. Of the remaining 115 studies, 99 were excluded as they were not RCT or metanalyses. The remaining 16 studies were vetted for relevancy to the research question 12 of which were excluded leaving 6 studies for the literature review. In the aromatase inhibitors and testosterone replacement search that yielded 41 studies only 1 study examined the coadministration of AIs and testosterone.

Literature Review

Pathophysiology of Hypogonadism in Males

Sizar & Scwartz (2020) state that 95 percent of the total testosterone in males is produced by the Leydig cells in the testicles. As previously mentioned, defects in the hypothalamic or pituitary region that cause hypogonadism is referred to as secondary hypogonadism. Conversely, defects that originate in the testicles which cause low testosterone are referred to as primary hypogonadism. It is therefore paramount to first distinguish which form of hypogonadism is present since treatments that enhance testosterone production in the testes would be futile if primary hypogonadism is present. Early morning total testosterone levels should be between 300 ng/dL and 1000 ng/dL. Hypogonadism is diagnosed when morning serum levels are less than 300 ng/dL. Elderly males should have a total testosterone level between 500and 800 ng/dL, whereas young adults should have a serum level between 600 and 900 ng/dL (Sizar & Schwartz, 2020)

The testosterone produced by the Leydig cells in the testes is brought about when Gonadotropin-releasing hormone (GnRH) is secreted by the hypothalamus which then stimulates the release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) by the anterior

pituitary. LH travels through the blood to the testes where it stimulates the testes to produce testosterone. Once produced, testosterone travels in the blood mostly bound to sex hormone-binding globulin (SHBG) with the remaining unbound testosterone circulating as free testosterone (FT). In the blood, testosterone can be converted into dihydrotestosterone (DHT) as well as Estradiol via the aromatase enzyme. Pitteloud et al. (2007) describe the controversy that surrounds the inhibition of testosterone production. Previous studies have reported that testosterone is responsible for LH inhibition while others have reported that estrogen is responsible for LH inhibition and therefore testosterone regulation. Pitteloud et al. (2007) were able to conclude that both testosterone and estrogen play a role in the regulation of testosterone. As a result, it is believed that testosterone inhibits GnRH production by acting on the hypothalamus; and estrogen, to a lesser degree, acts on the anterior pituitary to suppress LH.

By understanding the pathophysiology of the gonadal axis, clinicians can better execute the proper treatment regiments to mitigate the symptoms of hypogonadism. Additionally, knowing that estrogen is responsible for inhibiting LH, clinicians should be on guard and consider hyperestrogenism as a potential cause of hypogonadism. Along those lines, testosterone replacement therapy, AI's and SERMs can have effects not only on testosterone levels but on estrogen as well. TRT can raise estrogen levels, AIs can lower estrogen. Knowing this, it is equally important for clinicians to recognize the symptoms of excess estrogen because exogenous testosterone supplementation can further increase certain patient's hyperestrogenism; which in turn can contribute to gynecomastia, insulin resistance and weight gain. Through comprehension of the gonadal axis, clinicians can apply the results of the following studies and also recognize and test for unwanted side effects before they become problematic.

Efficacy of Testosterone Replacement Therapy in Hypogonadism

Ponce et al. (2018) published a systematic review and meta-analysis of randomized clinical trials to determine the effects of TRT on patient outcomes and adverse events in hypogonadal men. Within the study, four randomized control trials were selected from a group of 2,807 studies. The four studies that met inclusion and exclusion criteria included a total of 1,779 patients. The trials included adult men that had at least one symptom of hypogonadism and a baseline testosterone level <300 ng/dL. The duration of TRT within the trials ranged from 12 to 52 weeks.

When compared with the placebo in these studies, TRT was associated with a slight increase in sexual desire or libido with a standardized mean difference (SMD) 0.17; 95% CI [0.01, 0.34]; n = 1383, sexual satisfaction (SMD 0.16, CI [0.01, 0.31], n = 676) , and erectile function (SMD 0.16, CI, [0.06, 0.27], n = 1344). There appeared to be no effect on mood or energy. Patients receiving TRT had a higher incidence of developing erythrocytosis over the placebo group (RR 8.14, CI [1.87, 35.40] n = 1579). The study also revealed no correlation with TRT and increased lower urinary tract symptoms (Ponce et a., 2018).

Limitations of this study pertain to diversity in the cause of the hypogonadism amongst the subjects. Patients that had primary and secondary, as well as other causes of hypogonadism, were included in the study; which made it impossible to determine if TRT was more efficacious in specific types of hypogonadism. With regards to strength, the study's strict enrollment criteria provided more accurate results; in that patients who were not truly suffering from low testosterone and patients with comorbidities were excluded. This exclusion practice allows for a better representation of outcomes because results will not be skewed by adverse events that are secondary to other comorbidities.

The purpose of the study conducted by Magnussen et al. (2017) was to determine the effects of testosterone replacement therapy on total lean body mass, muscle function, and lean leg mass in aging men with type 2 diabetes. Thirty-nine men between the ages of 50-70 years with type 2 diabetes and secondary hypogonadism were enrolled in the study. Twenty of the patients received 50 mg of Testim testosterone gel supplementation and 19 received placebo for twenty-four weeks. The study used a double-blinded approach to measure the outcomes of therapy. Muscle mechanical function was measured using Nottingham Leg Rig aka leg extension power, isokinetic dynamometry which includes knee extensor maximal isometric contraction, rate of force development (RFD100) and maximal dynamic contraction (Dyn180). Physical function was measured by determining gait speed and body composition was determined through DEXA scan. Testosterone levels including free and total testosterone and with sex hormone-binding globulin (SHBG) were measured from fasting blood samples.

With the results of the study, the coefficient (b) represents the placebo-controlled mean effect of the intervention. Maximal isometric contraction (b = 18.4 Nm, p = 0.039); RFD100 (b = 195.0 Nm/s, p = 0.017); and Dyn180 (b = 10.2 Nm, p = 0.019), increased during TRT compared with placebo. There were no observed changes in gait speed or leg power. Total fat mass ($b = -1.3$ kg, $p = .009$) and leg fat mass ($b = -0.7$ kg, $p = 0.025$) decreased during TRT compared with placebo, whereas total lean body mass (b = 1.9 kg, p = .001) and lean leg mass (b = 0.5 kg, p < .001) increased. Total testosterone ($b = 14.5$ nmol/L, $p = 0.056$), BioT ($b = 7.6$ nmol/L, $p = 0.046$), and Free testosterone ($b = 0.32$ nmol/L, $p = 0.046$) increased during TRT compared with placebo, while sex hormone-binding globulin ($n = -2$ nmol/L, $p = 0.030$) decreased. Body composition improved while knee extensor mechanical function was preserved in the TRT group compared to the placebo group (Magnussen

et al., 2017).

The study's limitations included having a small sample size and the short duration of intervention. A longer duration study would be required to observe the long-term effect of TRT on muscle size and function. Another potential limitation is the unknown sleep cycles of both the placebo and testosterone group. Circadian cycles affect the levels of testosterone production with the peak occurring during the early morning. Although it is mentioned in the study that labs were drawn between 7:30 am and 9:30 am during the draw days, there is no mention if the participants slept through the night or during the day.

This study illustrates significant improvements in muscle mass, muscle contraction, lean body mass and bioavailable testosterone with testosterone replacement. More studies will be required to determine the long-term effects and determinants of testosterone replacement therapy in men with type II diabetes. At the present, it appears that testosterone replacement may be useful as an adjunct to help men with type II diabetes and low T in maintaining and or achieving an overall healthy body composition.

Storer et al. (2017) conducted a 3 year, double-blind, placebo-controlled, randomized trial of 256 healthy men over 60 years of age with testosterone levels between 100 and 400 ng/dL. The purpose of the study was to determine the effects of testosterone on muscle strength, power, fatiguability, physical function and lean muscle mass. Subjects were randomized and 135 were given 7.5g of 1% testosterone gel and 121 were given placebo gel for 3 years. The aforementioned muscle tests were performed at 6, 18 and 36 months. Muscle strength of the upper and lower extremities were measured via a one rep max of leg press and chest press exercise. Muscle power was measured using the same machines for the strength assessment. Subjects were performed 5 repetitions between 40%,50%, and 60% of their previously

established 1 rep max on the leg and chest press. The machines were equipped with instrumentation that measured the force and velocity of the exercise and therefore power. Muscle fatiguability was assessed through leg press and chest press exercises; wherein subject were ordered to perform as many reptations as possible until fatigue occurred. Physical function was measured via a timed stair climb of 12 stairs with one test assessing the subjects speed of climb and another weighted stair climb where the subjects carried 20% of their body weight. The subjects performed 2 trials of the unweighted stair climb with 2 minutes of rest between trials. The subjects then rested for ten minutes and then performed the weighted trials. Lean body mass was assessed using dual energy x-ray absorptiometry and associated lean body mass instrumentation.

The results showed testosterone administration for 3 years was associated with significantly greater performance in unloaded and loaded stair-climbing power than placebo (mean estimated between-group difference, 10.7 W [95% confidence interval (CI), −4.0 to 25.5], P = 0.026; and 22.4 W [95% CI, 4.6 to 40.3], P = 0.027), respectively. Changes in chest-press strength (estimated mean difference, 16.3 N; 95% CI, 5.5 to 27.1; P < 0.001) and power (mean difference 22.5 W; 95% CI, 7.5 to 37.5; P < 0.001). Changes in leg press power (mean difference 83.8 W; 95% CI, 35.4–132.2; P<0.001). The difference in leg press strength did not differ significantly between the two groups. Lastly, testosterone replacement was associated with an improvement in lean body mass (estimated mean difference [95% CI] between arms over 3 years, 0.9 kg [0.5–1.4 kg]; P < 0.001) (Storer et al., 2017).

There were no discernable limitations to the study, the ample sample size provided an adequate representation for the results of the study. The duration of the study demonstrated the long-term effects of testosterone supplementation on the aforementioned measurements of the

study. Finally, the assessments on muscle strength, power, fatiguability and lean body mass were conducted in a manner that accurately measures each individual parameter.

Kang & Li (2015) performed a systematic review and metanalysis to determine the effect of TRT on prostate specific antigen in men being treated for hypogonadism. Databases including Medline, Cochrane Library, EMBASE and Google Scholar were searched for applicable studies. Inclusion criteria consisted of randomized control trials wherein the intervention group received testosterone/androgen replacement and the control group received no treatment. Subjects included in the review had to have no history of prostate cancer. The primary outcome was a change in PSA levels during the course of treatment. Secondary outcomes were measured by elevated PSA levels after treatment and the number of patients who developed prostate cancer. During the analysis, 511 articles were identified; of which 15 studies with 739 patients that received testosterone replacement and 385 controls, were included. In 6 studies testosterone was administered transdermally, in 7 studies intramuscularly and in 2 studies orally. The duration of treatments ranged from 3 to 12 months.

The results of the analysis and systematic review demonstrated a higher PSA level in men receiving testosterone therapy compared to the placebo; with the difference in means of PSA levels = 0.154, 95% CI [0.069, 0.238], $p < .001$). The difference means of PSA levels were significantly higher for patients that received testosterone intramuscularly (IM) than the control group (difference in means of PSA levels = 0.271, CI [0.117, 0.425], $p < .001$). PSA levels after treatment were similar between the control and treatment groups (odds ratio [OR] = 1.02, CI [0.48, 2.20], $p = 0.953$). The difference in means of PSA levels were similar between patients who received testosterone transdermally and controls (difference in means of PSA levels = 0.085, 95% CI: −0.021 to 0.190, $P = 0.116$). The authors state that 3 studies were found that

provided data with respect to prostate cancer. Within these studies the development of prostate cancer occurred both in the control and testosterone groups; thus, a correlation between testosterone therapy and prostate cancer cannot be made. (Kang & Li, 2015).

There were some limitations of the research including variabilities in the populations examined, length of studies, testosterone replacement regimes, and baseline PSA levels in the studies. Again,It is also of note that three studies used to examine the risk of developing prostate cancer while on testosterone replacement were not sufficient to truly evaluate the risk of developing cancer. Further analysis of long-term testosterone therapy is required to adequately determine the effect that testosterone replacement has on PSA levels.

This analysis identified intramuscular testosterone replacement as a potential cause of elevated PSA levels in men. Knowing this may help providers choose alternative forms of therapy that do not affect PSA levels as drastically as IM injections. However, IM testosterone therapy is, at the present, the most affordable form of testosterone. With this in mind, perhaps alternative therapies like selective estrogen receptor modulators (SERMS)s may prove more beneficial therapeutically if they do not raise PSA levels as drastically as IM testosterone.

Efficacy of Selective Estrogen Receptor Modulators in Hypogonadism

Wiehle et al. (2014) set out to determine the effect enclomiphene citrate (Androxal), a SERM on men with secondary hypogonadism. The study was a randomized, phase IIB, double-blinded oral dosage, placebo-controlled, parallel, multicenter study; but open-label for the control comparator. Participants included 124 males in four treatment groups. One group would receive Androxal 12.5 mg daily, another would receive Androxal citrate 25 mg daily, another group would receive Testim testosterone gel; and the last would receive a placebo. The duration of the study was designed for 3 months. During the initial visit, participants were screened for

morning hormone levels as well as PSA, hematocrit, glycosylated hemoglobin, hemoglobin and sperm concentration. Men who had testosterone levels <250 ng/dL were enrolled immediately and men with testosterone levels >300 ng/dL were excluded from the trial. Men with testosterone levels between 250 and 300ng/dL were instructed to return at a later date to requalify.

The results of the trial showed an increase in testosterone after three months of therapy in both of the Androxal as well as the Testim cohorts. The group receiving Androxal 12.5mg showed an increase in total testosterone from 217.2 (SD 58.7) to 471.9 (SD 184.6). The group receiving Androxal 25 mg showed an increase in total testosterone from 209.8 (SD 55.4) to 405.8 (SD 162.8). The Testim group showed an increase in total testosterone from 210 (SD 54) to 462.6 (SD 289.0). The placebo group showed no increase in total testosterone from baseline. LH levels in the Androxal 25mg and 12.5mg groups were (9.5 ± 5.4 and 6.6 ± 4.4 mIU/mL) respectively, demonstrating Androxal's ability to preserve LH secretion. Of the 124 men that were enrolled in the program, only 73 completed the studies baseline and final sperm count analysis. The analysis found that 54% of the men in the testosterone group were oligospermic with sperm concentrations below 15 million/ml. Conversely, only 14.6% of subjects in the Androxal group were oligospermic after the end of the study (Wiehle et al., 2014). These results demonstrate testosterone's negative effect on fertility as well as Androxal's preservative effect on fertility.

The authors describe some limitations in the study which pertain to some of the participants failing to provide the four required semen samples throughout the study. Additionally, a study of a longer duration will be necessary to determine the long-term effects of Androxal on testosterone as well as male fertility. It is also unclear why prostate-specific-antigen levels were screened at the initial visit but not reevaluated at the end of the study.

Further research found a single-center, randomized, double-blind, placebo-controlled, parallel-group study conducted by Soares et al. (2018) which was done to examine the effects of clomiphene citrate on hypogonadism. The duration of the study spanned a total of 12 weeks. The purpose of this study was to determine the effects of clomiphene citrate on male obesity-associated hypogonadism. Seventy-eight men were enrolled aged 36.5 ± 7.8 years, with a body mass index >30 kg/m2 and total testosterone <300 ng/dL as well as symptoms reported from the Androgen Deficiency in Aging Males (ADAM) questionnaire on androgen deficiency. The ADAM questionnaire is a series of ten questions pertaining to libido, energy, strength, height, enjoyment of life, mood, erection quality, ability to play sports, and fatigue. Scores over 3 may indicate low testosterone. Percent body fat, skeletal muscle mass, and lean body mass were also assessed at baseline and again at 12 weeks. Secondary outcomes measured in the study consisted of hematocrit, prostate-specific-antigen (PSA) levels, and the international prostate symptoms score (IPPS). The participants were randomized and half were given 50 mg Clomiphene Citrate (CC) while the other half were given a placebo for 12 weeks.

The hormonal assessment results of the control group in the study showed an increase in total testosterone from 225.54±72.49ng/dL (n = 35) at baseline to 687.94± 276.66 ng/dL(n = 35) after 12 weeks. Free testosterone likewise increased 191.47±60.08 pmol/L (n = 30) to 565.97±217.93 pmol/L (n = 30). E2 increased from 32.48±12.59 pg/mL (n = 35) to 89.44±47.85 pg/mL (n = 35). LH increased from 4.25±1.81IU/L (n = 35) at baseline to 9.75±4.75 IU/L (n = 35) after 12 weeks. FSH increased from 4.13±2.77 IU/L (n = 35) to 9.36±5.81 IU/L(n = 35). SHBG had a slight increase from 21.55±7.86 nmol/L (n = 35) to 29.48±9.79 nmol/L (n = 35). A P value of (P<.001) was recorded for all the previously mentioned hormone parameters. All parameters in the control group remained unchanged from baseline (Soares et al., 2018).

The ADAM questionnaire results after 12 weeks of CC demonstrated a significant reduction in patient scores in both groups. The CC group had 5.26 ± 2.67 positive questions at baseline and 3.38 ± 2.74 positive questions at week 12. Conversely, the placebo (PLB) group had 5.00 ± 2.15 positive questions at baseline and 3.12 ± 2.63 positives at week 12 with (P = 0.229) (Soares et al., 2018). The results of both groups experiencing reductions in the ADAM questionnaire cannot be readily explained.

Lean body mass increased from 70.11±10.11 kg (n = 37) in the CC group to 72.32±9.66kg (n = 37) at 12 weeks; whereas the PLB group decreased from 71.00±11.98 kg (n = 34) at baseline to 70.89±12.05 kg (n = 34) at 12 weeks (p<.001). Skeletal muscle mass in the CC group increased from 42.39±5.73 kg (n = 37) at baseline to 43.43±5.74 kg (n = 37) at 12 weeks (p<.001). Skeletal muscle mass in the PLB group remained largely unchanged. Lastly, percent body fat in the CC group decreased from 46.54±5.97% (n = 37) at baseline to 46.05±6.20% (n = 37) at 12 weeks; whereas in the PLB percent body fat increased from 45.93±6.70% (n = 34) to 46.02±6.57% (n = 34) at 12 weeks (p=.073) (Soares et al., 2018).

PSA levels increased in the CC group from 0.62±0.41mg/dL (n = 33) at baseline to 0.76±0.48mg/dL (n = 33) at 12 weeks. IPPS scores had no significant changes in either the CC or PLB groups. These findings suggest that while PSA levels showed significant increases in the CC group, there were no significant increases in lower urinary symptoms (Soares et al., 2018).

There were several limitations in the study including several participants that dropped out; though none from adverse effects. The reduction in participants diminishes the already small sample size of patients which could inadvertently skew results. The short duration of the study did not allow for the long-term efficacy of CC to be established. Further studies of longer

duration will be necessary to determine if the short-term benefits of CC will be able to be maintained over a long period of time.

These results are useful in that they further demonstrate the efficacy of SERMs for use in men with secondary hypogonadism. It provides insight into SERMs ability to mitigate androgen deficiency symptoms. SERMs may prove superior to testosterone therapy especially in men with obesity and increased levels of estrogen as well as those men who want to preserve their fertility.

The Efficacy of Coadministration of Aromatase Inhibitors and TRT

Mechlin et al. (2014) performed a study to determine the efficacy of the coadministration of Anastrozole an AI, with testosterone pellet therapy. The design of the study was comprised of a single-centered retrospective analysis of 38 hypogonadal men. Twelve of the men were given Anastrozole 1 mg daily along with a standard dosing of testosterone pellets placed under the skin. The second group received only testosterone pellets subcutaneously. The group's blood levels of total testosterone, free testosterone, E2, SHBG, LH, and FSH were evaluated at baseline and at six and 15 weeks of therapy.

The results of the study demonstrated significantly higher levels of total and free testosterone in the testosterone pellet/Anastrozole group than the testosterone pellet group at > 120 days ($p < .05$). The testosterone pellet group had significantly higher levels of E2 throughout the duration of the study ($p < 0.01$). Gonadotropin levels remained stable in the testosterone/Anastrozole group for the duration of treatment, thus preserving fertility. The testosterone pellet/Anastrozole group had an average reinsertion time of 198 days, whereas the testosterone pellet group averaged 128 days between reinsertion of pellets.

There were several limitations in this study including a relatively small sample size of patients. There was no evaluation on the therapies effect on any physical strength, muscle mass,

lean body mass, libido or mood. Therefore the study could not be used to draw any conclusion with the other forms of therapy. Furthermore, there was no mention of randomization or how it was determined which patients received Anastrozole with treatment, which leaves room for bias amongst the researchers. Adverse effects and reports of changes in symptoms of hypogonadism were also not included.

Discussion

The diagnosis and treatment of hypogonadism is far more complex than many providers realize. Differentiation of primary and secondary hypogonadism in the diagnosis is paramount when selecting treatment options. When primary hypogonadism is identified only TRT will suffice as a viable treatment. Conversely, in the case of secondary hypogonadism, treatment options in the form of TRT, AI's and SERMS all have potential for being employed as treatment modalities. Providers must resist the urge to test only free and total testosterone levels so that proper identification of the form of hypogonadism can be accomplished. In addition to the aforementioned blood tests, blood levels of LH, FSH and estradiol should be examined. Although rare, hyperestrogenism can also be a cause of low testosterone, especially in obese men. Furthermore, providers should consider monitoring estradiol and testosterone levels in men during hormone replacement therapy due to the fact that TRT can significantly increase estrogen levels in men and can contribute to unwanted side effects such as gynecomastia.

Efficacy of Testosterone Replacement Therapy in Hypogonadism

The study conducted by Andersen (2019), determined TRT has merit with regard to increases in muscle mass, muscle contraction and lean body composition. TRT even in the short term of six months can help patients increase and maintain their physical strengths. Ponce et al

(2018) further support the efficacy of TRT by describing increases in sexual desire, sexual satisfaction and erectile function in patients receiving TRT. The increased incidence of erythrocytosis noted by Ponce et al (2018) is a well-known potential side effect of TRT and is easily managed. Providers should not be dissuaded from using TRT but should rather routinely screen for erythrocytosis during their patient's therapy. Magnussen et al. (2017) found that testosterone therapy was effective at increasing lean body mass, lean leg mass and muscle function. Their findings support the use of TRT for attenuating some of the symptoms of decreased physical function and loss of muscle mass that are associated with hypogonadism. The 3 year, double blind, placebo controlled, randomized trial of 256 healthy men by Storer et al. (2017) correlated an increase in muscle strength, power, fatiguability, physical function and lean muscle mass with TRT. The long duration of the study provides insight and support in regards to the long term efficacy of TRT. Kang & Li (2015) studied the correlation between elevated PSA levels in TRT and determined that the use of intramuscular testosterones was associated with the greatest increase in PSA levels over other forms of TRT.. Knowing this, providers should consider monitoring TRT patients for increased PSA levels and prostate symptoms when intramuscular testosterones are used. Additionally, Kang & Li (2015) found three studies that provided data on prostate cancer and TRT. The studies found that the rates of prostate cancer were similar between the treatment and control groups. It is apparent that further studies are necessary to examine any correlation between prostate cancer and TRT.

Efficacy of Selective Estrogen Receptor Modulators in Hypogonadism

Wiehle et al. (2014) analyzed the efficacy of SERMs and determined they were effective at increasing testosterone levels while also preserving male fertility. The construct of the study contrasted the SERM Androxal with the testosterone replacement medication Testim. The results

demonstrated how TRT negatively impacts spermatogenesis. Conversely, the use of SERMs not only raised circulating testosterone to a similar level as Testim, but also preserved sperm production and fertility. These results are important when considering treatments in hypogonadism as some men will desire to maintain their fertility during therapy. The study conducted by Soares et al.(2018) evaluated the use of the SERM clomiphene citrate (CC) on hypogonadism. Although the study was brief, only lasting 12 weeks, the results demonstrate the ability of SERMs to increase testosterone levels. The study also showed an improvement in libido, energy, strength, enjoyment of life, mood, erection quality, and fatigue through the ADAM questionnaire. Furthermore, the use of CC was associated with an increase in lean body mass and skeletal muscle mass as well as a decrease in percent body fat. PSA levels did rise in the CC group just as is seen in TRT; however, there were no reports of lower urinary symptoms by any test subjects. These results parallel those seen in TRT making it difficult to discern which treatment modality is the most effective for the treatment of hypogonadism.

The Efficacy of Coadministration of Aromatase Inhibitors and TRT

Mechlin et al's research regarding the coadministration of testosterone pellets and Anastrozole demonstrate the augmentation effect Anastrozole has on testosterone. As mentioned in the study, participants using the coadministration of the aforementioned medications experienced a longer duration between the reapplication of testosterone pellets and a significant increase in testosterone levels in those patients. These results might suggest that when Anastrozole is used in conjunction with testosterone, higher levels of testosterone can be achieved and maintained for a longer duration through aromatase inhibition. There was no mention of any assessment of physical function, mood or libido which makes it impossible compare this data with any of the information on TRT and SERMs Furhermore, no other studies

on the coadministration of TRT and AIs could be found during the literature review. Without further research no conclusions can be drawn as to the efficacy of this therapy.

Conclusion

In the treatment of hypogonadism, it is important to consider the causative factors when determining which treatment modality to use. In primary hypogonadism where testicular failure occurs, only TRT will be an effective therapy. Secondary hypogonadism can have various causes that can impact what treatments are prescribed to manage each patient. TRT is efficacious at managing the symptoms of hypogonadism. However, providers must be aware of the increased incidence of polycythemia and infertility that are associated with the treatment. SERMs are also effective at managing secondary hypogonadism with improvements in muscle mass, lean body mass and libido similar to that of TRT. Additionally, SERMs preserve male fertility and are relatively inexpensive as they are generic. Finally, AIs such as Anastrozole in combination with testosterone have been shown in one study to improve the effectiveness of TRT. However, only one study on the coadministration of TRT and AIs could be found in the literature review. Therefore, no conclusions can be made as to the efficacy of this treatment regiment until further research can be conducted. In the comparison of TRT and SERMs neither treatment modality could be proven more effective over the other. Soares et al. (2018) and Storer et al. (2017) both describe and quantify the physical improvements TRT and SERMs had on patients. However, the two studies varied greatly in duration, making it difficult to draw any conlusion as to which one is more efficacious. Apart from the preservation of fertility, SERMs and TRT both appear to be efficacious at attenuating the symptoms of hypogonadism. Further RCTs are necessary to test which form of therapy is superior.

Applicability to Treatment

With the advent of new therapies and treatment options, managing hypogonadism can be difficult. The information provided by this literature review will help providers in determining which treatment modality is the most appropriate to treat their patients' hypogonadism. This literature review also provides a clear explanation on how TRT and SERMs are both useful for treating hypogonadism.

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