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Comparison of short and long-acting testosterone replacement therapy for better sperm production and testosterone levels in male late-onset hypogonadism

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***Abstract*---**Introduction: Testosterone Replacement Therapy (TRT) is the standard treatment for male late-onset hypogonadism. Short-acting and long-acting testosterone are currently available treatments and have been approved by the Food and Drug Administration (FDA). The administration of exogenous testosterone is known to increase sperm production and T levels in men suffering from late-onset hypogonadism. However, limited research compares the efficacy of these two types of TRT. Objective: This study aims to compare the efficacy of short-acting and long-acting testosterone replacement therapy on sperm production and T levels in men suffering from late-

onset hypogonadism. Methods: We searched for electronic databases including PubMed, Cochrane Library, EMBASE, Scopus, Web of Science, Allied and Complementary Medicine Database (AMED), and Google using keywords. All studies were evaluated by three independent reviewers who resolved differences by consensus. Results: We identified 21 studies that met our inclusion criteria. After applying the inclusion criteria, only 21 database sources remain for further analysis. Conclusion: Long-acting formulas affect blood more. RCTs show TU boosts libido and testosterone. Male infertility may result from long-acting TU blocking LH and FSH. TRP improves erections by increasing motile sperm and libido. Peanut allergy-related short-acting TRT causes nausea, itching, and injection-site pain. Due to less frequent doses, long-acting TRT is preferable to short-acting TRT. Late-onset hypogonadism's testosterone symptoms are more stable. Long-acting testosterone can cause infertility.

***Keywords*---**hypogonadism, testosterone, male infertility, late-onset hypogonadism.

Introduction

Reason

A systematic review was conducted to compare the effects of short-acting and long-acting testosterone replacement therapy (TRT) in men suffering from late-onset hypogonadism. Testosterone replacement treatment aims to increase testosterone levels in the bloodstream and alleviate symptoms. (1) Low testosterone levels can cause a variety of symptoms, including fatigue, depression, loss of muscle mass and bone density, erectile dysfunction (ED), and low libido. Therefore, testosterone replacement therapy is an effective treatment for late-onset hypogonadism. However, two different types of TRT can be used to treat this condition: short-acting and long-acting testosterone replacement therapy (TRT). One short-acting TRT be composed of testosterone propionate, testosterone phenylpropionate, testosterone isocaproate, and testosterone decanoate as we can see in figure a. One of the long-acting TRT is testosterone undecanoate (TU) as we can see in figure b. Both forms of treatment aim to increase testosterone levels in men who have late-onset hypogonadism, but they differ in how quickly they work and how long their effects last.

The literature review has identified that current evidence on the use of long-acting testosterone replacement therapy is scarce, while studies on short-acting therapy abound. (2) However, there has been no systematic review comparing these two types of treatment. Based on this limited evidence, this review compares the effectiveness of short- and long-acting testosterone replacement therapy for patients suffering from male late-onset hypogonadism. Significantly, the results of this review will provide insight into which treatment options are more effective, as well as whether there are significant differences between them. The novelty of this manuscript is that it is the first systematic review of clinical studies on the

effects of short-acting and long-acting testosterone replacement therapy in men suffering from male late-onset hypogonadism.

Purpose

This systematic review aims to compare the effectiveness of short-acting and long-acting testosterone replacement therapy (TRT) on sperm production and T levels in men suffering from late-onset hypogonadism.

Methodology

Inclusion Criteria

A systematic review was conducted using PRISMA guidelines. Randomized controlled trials (RCTs) comparing short-acting and long-acting TRT with placebo, no treatment, or other active interventions for patients with male late-onset hypogonadism were included. In addition, we included a randomized controlled trial (RCT) that compared short-acting (1 week to 6 months) and long-acting (6 months or more) administration of testosterone replacement therapy in men with male late-onset hypogonadism. From the initial search, 9 RCTs met the inclusion criteria.

Sources of Information

Searched databases include PubMed, Cochrane Library, EMBASE, Scopus, Web of Science, Allied and Complementary Medicine Database (AMED), and Google Scholar. The sources consulted are only those that are relevant to the study. The date when each source was last searched or consulted is August 8, 2022.

Search Strategy

The search strategy for this paper is based on a broad literature review using keywords. The search is carried out using the following terms: testosterone, male infertility, sperm production, testicular function, and late-onset hypogonadism. The keywords used for each search are: "testosterone replacement therapy" OR "testosterone supplementation" OR "testosterone deficiency" OR "control gate of authority" OR "hormone replacement therapy" OR "hormone replacement therapy."

Selection Process

For this review, the researchers used a systematic approach to identify relevant studies focused on short-acting and long-acting testosterone replacement therapy for male infertility. The researchers reviewed all studies published between January 1, 2000, and July 31, 2022, which reported sperm production or steroidogenesis as interesting results in men with late-onset hypogonadism. We extracted data from this study on their methods for predicting the effect of T replacement therapy on sperm production or steroidogenesis in men with late-onset hypogonadism; we also extract information about their methods to determine if a study meets our inclusion criteria. We do not use automated tools

to extract data from our electronic databases; instead, we review each record manually.

Data Collection Process

Three reviewers independently extracted data from the studies included in this review, using the standard form. The disagreement was resolved by discussion with a third reviewer, who was also involved in the data extraction process. The data extraction form includes information about the study design, participants, interventions, the size of the results, and the analysis methods used for each type of intervention (short-acting vs. long-acting). All three reviewers independently extracted data from the study.

Item Data

Short-acting T replacement therapy (SART) was studied to determine its efficacy in increasing sperm production and steroidogenesis in men with late-onset hypogonadism. The use of SART was associated with an increase in sperm count and motility when compared to placebo treatment. Long-acting T replacement therapy (LART) was studied to determine its effect on increased sperm production and steroidogenesis in men with late-onset hypogonadism. LART was found to increase sperm count and motility when compared to placebo treatment. Secondary outcomes were changes in body composition, libido, mood, energy levels, sexual function, sleep quality, bone mineral density (BMD), and general health.

Bias Assessment Risk Study

The tool used to assess the risk of bias is the Cochrane bias risk tool. For each domain, there is no difference of opinion between reviewers about the assessment. Two reviewers independently assessed all studies using this tool, with data extracted independently from each study.

Effect measure

In this study, the measure of effect used in the synthesis or presentation of results was the ratio of risk and the average difference. The risk ratio is a measure of the relative risk of an outcome (increased sperm motility) with treatment (testosterone replacement therapy) compared to the control group (placebo). The average difference is a statistical measure of the average change in results for participants receiving one treatment compared to another (testosterone replacement therapy).

Synthesis Methods

The first step in synthesizing literature is to identify data that can be synthesized. It involves the identification of studies that are similar in design, results, and size of effects. The study intervention was tabulated, and any differences between the planned groups were identified.

Bias Assessment Reporting

In this review, the risk of reporting bias due to missing data is assessed by conducting a systematic search of the relevant literature and assessing the size of each study. The risk of publication bias was also assessed by comparing the results reported in more than one study. There is no evidence of reporting bias or publication bias in any report.

Certainty Assessment

This review considers all relevant trials (to ensure that they are of high quality and have similar designs) and assesses their quality using the Cochrane Collaboration (CoC) toolkit. The reviewers also assessed the completeness of the reporting using PRISMA guidelines and conducted sensitivity analyses as necessary.

Result

Study Selection

The number of records identified in the search is 720. Five hundred sources were sourced from the study database, 200 from the register, and 20 sources were identified from websites, organizations, and citation searches. After applying the inclusion criteria, only 20 database sources and five report studies remain for further analysis. The selection process involves reading titles and abstracts, downloading the full text as needed, and checking references for more information about each study. A summary of the election results is presented in the PRISMA diagram (see figure 1). The study characteristics of individual studies are also provided in table 1.

Synthesis Results

Bias risk for each study was assessed using the Cochrane Collaboration tool to assess the risk of bias in a systematic review (ROBIS II). The findings suggest that there is a low risk of bias in all 21 studies included in this review.

Table 1: Individual Study Results

S/N	Study Included	Study Design	Sample Size	Formulation T	Result
1.	Corona et al. (2020)	Expert group analysis	-	contraindications and monitoring of short and long-acting TRT	Improvement of sexual function in short-acting and long-acting TRT
2.	His (2000)	Rct	76	Testosterone oral undecanoate for 12 months	No significant difference between placebo and testosterone group
3.	Richardson et al. (2007)	Rct	13	Intramuscular and oral injections enter letrozole for 6 weeks	Increased luteinizing, hormones, and testosterone levels. The overall increase in sexual desire
4.	Mulhall et al. (2016)	Rct	1075	12 weeks treatment with Oral Tadalafil	Testosterone is low, with high levels of LH. No statistical differences in treatment groups
5.	Cunningham et al. (2015)	cross-sectional study	788	T trial	Increased sexual desire - increased sexual levels and libido
6.	Anderson (1992)	Rct	31	Testosterone enanthate (TE) for 8 weeks	Increased plasma testosterone – Increased sexual desire
7.	Hohl (2009)	Rct	50	Deposteron – 4 weeks Durateston-4 weeks Nebido-12 weeks	Increased testosterone levels. TU shows higher clinical effectiveness
8.	Hong (2002)	Rct	28	TU Oral	Increased testosterone levels
9.	T'Sjoen (2004)	Pilot study	161	Scale AMS	AMS rankings and other health assessment findings show a significant relationship, although no sub-scores for the last survey were associated with plasma concentrations of testosterone.
10.	Wang (2018)	Rct	470	T trial	Positive correlation in PDQ DISF-II advertising. Increased sexual desire in the T-trial compared to the placebo group
11.	Hackett et al. (2013)	Rct	211	Testosterone Undecanoate – 30-52 weeks	TU improves sexual function, desire, and satisfaction of sexual intercourse. P=0.005. Longer prolongation of enhanced sexual function
12.	Ramasamy et al. (2020)	Rct	60	Nasal testosterone (Natesto)-6 months (short-acting)	Increased levels of testosterone – sexual desire and satisfaction. The number of motile

S/N	Study Included	Study Design	Sample Size	Formulation T	Result
					sperm retained in
13.	Guidry et al. (2018)				
14.	Pastuszak et al. (2015)	Rct	178	T gel, T pellets, and injectable T	Increased serum levels in both treatments ($p<0.0001$)
15.	Morgentaler Et al. (2008)	Rct	130	TU -24 weeks	The normal range of serum testosterone levels reached at week 10
16.	Diaz et al. (2022)	Rct	75	Testosterone Pellets, Intranasal Testosterone and Testosterone Cypionate	Long-acting formulations have a higher impact on serum levels compared to short-acting formulations
17.	Bhasin et al. (2018)			consensus-based assessment	Consistent monitoring of treatments to prevent side effects of long and short T therapy
18.	Hellstrom et al. (2021)	Rct	44	Intranasal Testosterone Short Work	An increased score of erectile function index-motile sperm count, and LH increased at short work
19.	Kresch at al. (2021)	Rct	300	Intratesticular T and exogenous T	Short and long working T shows a statistical decrease in serum 17-hydroxyprogesterone
20.	Kavoussi et al. (2022)	Rct	27	Natesto T	Reducing the E2 level
21.	Donatucci et al. (2014)	Rct	15,345	Long-lasting topical TRT and short TRT-30 recipes	The same results in discontinuation of therapy decreased long and short injections by about 40-50%

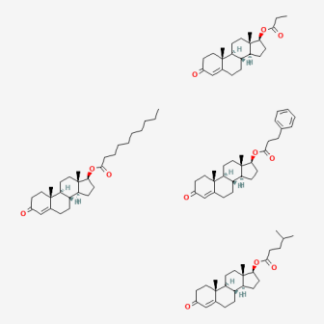
Discussion

Scholars have long suspected that inhibition of the hypothalamic-pituitary-gonadal axis occurs when hypogonadal men take long-acting testosterone replacement drugs. (5-8) Treatment of short-acting testosterone therapy, on the other hand, appears to have a smaller influence on the hypothalamic-pituitary-gonadal axis than long-acting TRT in the regulation of increasing spermatogenesis, according to this latest study. (11) In most men, Natesto, acting short, seems to increase testosterone levels while preserving semen parameters. (14-17) Men diagnosed with operational late-onset hypogonadism who want to maintain normal sperm parameters can benefit from therapy with Natesto because it can be efficient and safe. (14). Consistent findings suggest that short-acting T treatment, consisting of multiple T doses with a shortened half-life

spread throughout the day, reduces the suppression of the HPG axis and limits the amount of damage to spermatozoa.

TU (Long-acting) and Short-acting TRT Mechanism

The molecular weight of TU, a semisynthetic systemic androgen, is 456.7 Da. (26) The lipophilicity of its status as a fatty acid ester means it is absorbed slowly. Because Nebido (TU) is a broader side chain and hydrophobic (11 carbon atoms against 7 in other esters; see Figure a), its half-life is greater than that of other testosterone preparations. (26) In contrast, short-acting TRT has four esters of testosterone. Each ester has its unique duration of action (see figure 2b). When the esters reach the bloodstream, they are hydrolyzed to release testosterone.



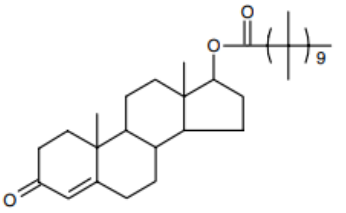


Figure a. *Carbon Structure of Short-acting TRT 250 (28)* **Figure b.** *TU carbon structure (26)*

To create a physiologically inert pro-drug, testosterone is esterified at its 17 -hydroxyl group with fatty acid esters of varying aliphatic or other chain lengths (see figure 3). (29) Injecting testosterone ester in an oil carrier profoundly into a muscle creates a local drug depot from which the testosterone ester is released at a slow pace defined by its Physico-chemical partitioning according to the testosterone ester's hydrophobic nature. When testosterone reaches the extracellular fluids, it is quickly digested by ubiquitous non-specific esterases and enters the bloodstream free of its ester. (29)

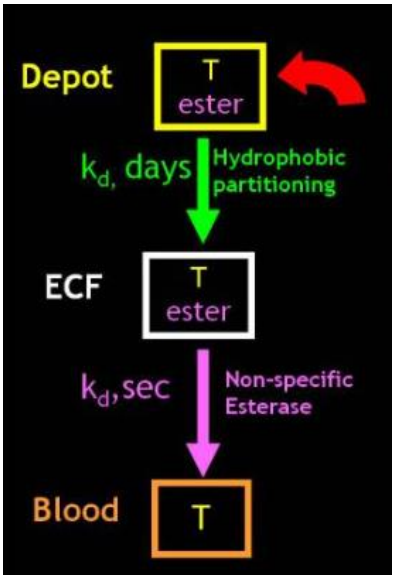


Figure 3. Mechanism of depot injection

The benefit of using a shorter-acting version of T therapy that the FDA is authorized to maintain a body temperature that more closely resembles the physiological function over the long-acting version is that it shows significant promise in the treatment of men with low testosterone. (10) Additionally, when compared to the composition of longer-acting testosterone, short-acting testosterone delivery methods, such as nasal delivery, do not seem to have any effect on 17-OHP blood. (20) This also agrees with previous research conducted by other authors. (18-20) It is important to note that these results may not apply to all patients suffering from male late-onset hypogonadism. Specifically, it should be borne in mind that individuals who experience severe late-onset hypogonadism tend to require more attention than those who have less severe symptoms to achieve therapeutic goals such as improving the quality of semen or sperm count. (22).

At the follow-up point, a substantial increase in blood sperm count is noticeable across the board for all treatment methods. (20) Diaz et al. (2022) concluded that Hypogonadal men who received TRT and wanted to protect their reproductive potential in the best possible way might find that NT and other short-acting versions of testosterone were beneficial for them. (19) On the opposite side, Morgentaler et al. (2008) concluded that when administered intramuscularly, TU provides sustained and consistent blood testosterone levels within the normal range for ten-week dose intervals. (17) This approach to long-acting testosterone therapy expands the optimal treatment dosing interval beyond existing injectable androgen treatments. In addition, it offers potentially acceptable prospects for daily use of transdermal gels or patches. In men who are experiencing late-onset hypogonadism, therapy with TU seems safe, well tolerated, and a practical option. Most importantly, Kavoussi et al. (2022) have established that fertility can be maintained in many men when they begin therapy with the latest short-acting intranasal androgen gel. (24) This applies even to men who have never been

treated before or after the washing period of the long-working TRT method. Additionally, it has been shown that most men who switch from long-acting TRT to Natesto can maintain their testosterone production, maintain reduced E2 levels, and have increased libido. (16)

However, according to Bhasin et al. (2018), the first diagnostic test should include a measurement of total testosterone levels in the morning of fasting using a proper and trustworthy test. The authors further suggest verifying the diagnosis by repeating the total T-level test taken in the early hours of the morning when the patient was fasting. (20) It is recommended by Bhasin et al. that men whose total T is close to the normal lower threshold obtain free T density by equilibrium renal replacement therapy or by assessing it using the appropriate formula. These are recommendations made by researchers.

On the other hand, there are some side effects of TRT, such as decreased T levels of intratesticular, azoospermia, infertility, and atrophy of testicular. Azoospermia and Atrophy of testicular because of suppression effect from exogenous T on the hypothalamic-pituitary-gonadal axis via a negative feedback mechanism on it. (29). Azoospermia occurs after 6 months of TRT in up to 65% of men who had weekly intramuscular injections of 200 mg T enanthate, while the volume of the testis can decrease by 23%. (30). TRT can provide several advantages as well as risks for men who are treated to normalize and improve their deficiency of T levels. The mechanism of action of exogenous TRT is to restore the T levels. Multiple routes of administration depend on patient preference and needs. It can be administreted via oral, buccal, intramuscular, transdermal, subdermal, and nasal preparations. Besides these advantages, exogenous TRT gives some risks and limitations such as decreasing Intratesticular T, disturbing spermatogenesis, and male infertility. (31, 32, 33, 34)

Conclusion of the Study

In summary, the review established that long-acting formulations have a higher impact on serum levels compared to short-acting formulations. The TU formulation shows a normal range of serum testosterone levels in various RCTs as well as increasing sexual desire. Conversely, long-acting use of TU can suppress the production of luteinizing hormones and FSH which can result in male infertility. TRP shows an improvement in erectile function indicated by an increase in the number of motile sperm as well as an increase in libido levels. Challenges associated with short-acting TRT include peanut allergies that can cause nausea, itching, and pain at the injection site. Overall, this evaluation favors long-acting TRT over short-acting TRT due to the convenience of less frequent doses, which allow patients to go about their normal day without having to stop to inject themselves. Due to the body's various responses to testosterone levels, people with late-onset hypogonadism will have fewer 'up and down' in their symptoms. nevertheless, in men who use testosterone long-acting, it can result in sperm parameter values that tend to deteriorate and experience infertility in men.

Limitations of the review process used

The review process used in this article is valid, and its conclusions are supported by evidence. The authors were able to synthesize the results of several studies on this topic, which is not an easy task. They can do it with many subjects, which is the power of research. The limitations of the review process include its reliance on self-reported results and the possibility that there may be a publication bias towards negative results. Another limitation is that studies are included based on relevance rather than quality, which means some of them may not be excellent studies. This could affect the results, which would make it difficult to conclude them.

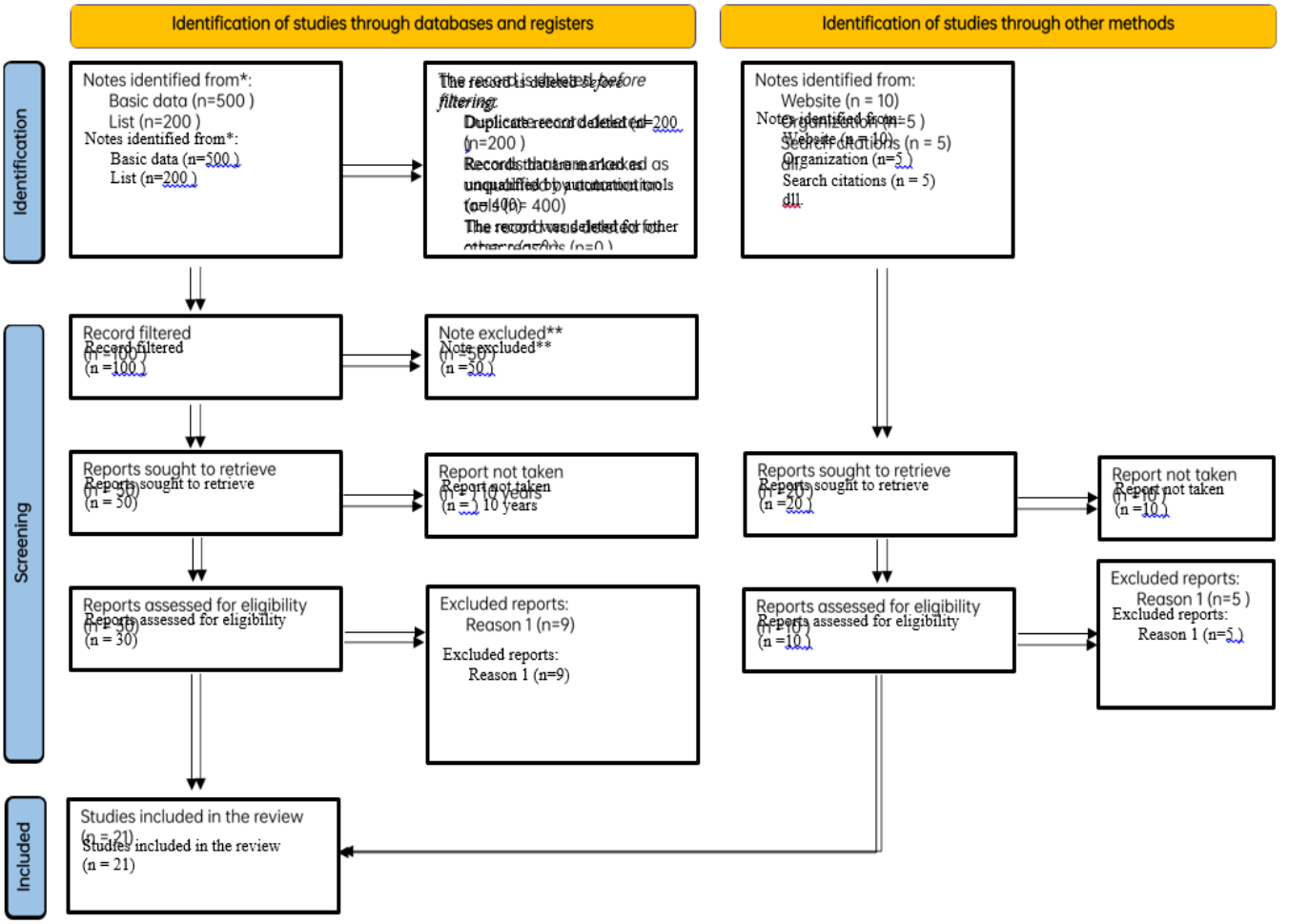
Implications for future research

Long-acting TRT is more effective in preventing low testosterone levels from rising, which can lead to infertility. Therefore, the findings of this study have implications for future practices, policies, and research. In terms of policies and practices, this research should be useful for providers who make decisions about which type of TRT to prescribe for their patients. The findings could also guide healthcare providers on how best to educate patients about TRT options. Future research should focus on determining whether there is a difference in effectiveness between short-acting and long-acting TRT for men with low testosterone levels.

Other Information

An online version of this article is not yet available. Before the start of this research project, the authors of this review did not have any conflicts of interest that needed to be disclosed. The researchers themselves stepped onto the plate to bear the cost of this study. During this investigation, every necessary medical consideration that has been imposed is adhered to in the letter.

Figure 1a: PRISMA Diagram Showing Filtered Sources



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