Journal of Urology and Renal Diseases
Yassin A, et al. J Urol Ren Dis 10: 1413.
www.doi.org/10.29011/2575-7903.001413
www.gavinpublishers.com
Review Article

Recent Update on Advancements in Testosterone Therapy (TTh)

Aksam Yassin[1,2,3*], Osama Asaad[4], Hatem Kamkoum[1], Raidh Talib Alzubaidi[1,2], Ahmed Ramadan[5], Hasan Abdallah[1], Abdulla Al Ansari[1,2]

[1] Hamad Medical Corporation, Aisha Al Attiyya Hospital, Andrology & Men's Health Unit, Qatar

[2] Weill Cornell Medical School NY, Qatar

[3] Dresden International University, Preventive Medicine Program, Dresden Germany

[4] Hescuro klinik, Department of Urology, Bad Bocklet, Germany

[5] Pharmacy Department, Aisha Al Attiyya Hospital, Qatar

***Corresponding author:** Aksam Yassin, Hamad Medical Corporation, Aisha Al Attiyya Hospital, Department of Surgery, Andrology & Men's Health Unit, Qatar

Citation: Yassin A, Asaad O, Kamkoum H, Alzubaidi RT, Ramadan A, Abdallah H, Al Ansari A (2025) Recent Update on Advancements in Testosterone Therapy (Tth). J Urol Ren Dis 10: 1413. DOI: 10.29011/2575-7903.001413.

Received Date: 02 March 2024; **Accepted Date:** 07 March 2024; **Published Date:** 10 March 2024

Abstract

Objectives: Low testosterone levels (hypogonadism) is associated with several clinical abnormalities, including sexual dysfunction, obesity, decreased muscle mass and strength, diabesity, and decreased bone density. There is a transition in the concept from sexual steroid hormones to metabolic hormones as well, so that testosterone deficiency can be considered a systemic disease affecting multiple organ systems. The use of TTh aimed to restore serum testosterone levels to physiological serum concentrations using variety of preparations where many of these signs can be relieved. The development of Gels and long-acting injectable formulations with steady state serum level in the last two decades gave rigor and most useful treatment options. This paper reviews the latest innovations or advances of current testosterone treatments including their advantages, drawbacks and addresses important issues in TTh.

Methods: This review was conducted according to the Preferred Reporting Items for Systemic Reviews and Meta-Analyses (PRISMA) guidelines. The PubMed, Medline, Scopus and Cochrane databases were searched using the following keywords ("testosterone" or" Testosterone replacement") AND "diabetes" OR "Prostate" "prostate cancer" OR "interrupted" OR "interruption" OR "LUTS" OR "cut-off" OR "reference range". Studies recruited were screened for inclusion criteria which included studies discussing one of the 4 objectives of the systematic review: 1. Cut off references, 2. Prevention or even remission of type II Diabetes Mellitus, 3. Intermission of treatment and 4. Prostate, LUTS, Prostate Health or Cancer. The search was limited to the past 15 years. Animal studies, case reports and studies not written in English were excluded. Screening was done by 2 researchers individually. In case of discrepancy between them, a senior researcher would review it.

Results: The initial literature search retrieved 393 studies. After screening 4 studies were removed due to duplication, 360 studies were further excluded after reviewing the title, abstract or the whole manuscript due to different exclusion criteria or being not focused on the objective. 29 studies were included in the review. 1 study discussed the cut-off value, 4 studies discussed the effect of testosterone replacement on control of type II diabetes mellitus, 4 studies on interruption of testosterone replacement and 20 studies discussed effect of testosterone replacement on prostate.

Conclusions: Numerous studies have demonstrated the benefits of TTh overtly hypogonadal men. There are several possible administration routes for testosterone treatment. Each approach has advantages and drawbacks, and the choice of the method of replacement will often be determined by patient preference or co medication (no im injections in patient under Cumarin or similar anticoagulants. Although new developments are promising, it seems that, among the available treatments, only transdermal gels delivery and long-acting injectable TU have provided pharmacokinetic behavior that is giving steady state level within physiological range

Keywords: Advances; Aging Male; Diabetes; Hypogonadism; Innovations; Late Onset; Obesity; Prostate Health; Prostate Cancer; Sexual Health; TTh

Introduction

During the last two decades, there has been a revolution in therapeutic treatment options to provide healthcare providers and their hypogonadal patients with the best treatment option aiming to restore serum testosterone levels to physiologic serum concentrations. Different therapeutic options were reported from implanted testosterone pellets to injectable testosterone esters, short and long acting and then to oral methyltestosterone. The first-generation oral Testosterone Undecanoate (TU) product then to scrotal and non-scrotal testosterone patches and then to topical testosterone gels [1]. Other recent TRT innovations include a long-acting testosterone undecanoate injection (intramuscular) and a short-acting testosterone enanthate injection (hypodermal) [2] and a nasal testosterone gel, which could not be well established in use. The oral soft gel formulation of testosterone undecanoate is the latest innovation in TTh and recent reports on phase-III clinical studies have been published so far and showed how this new formulation is safe and effective as a therapeutic in the treatment of men with hypogonadism [3]. Two synthetic paths were used to make the oral testosterone: the alkylation of the C-17 position using chemical modification of testosterone, to make the tertiary alcohol derivative, 17 α-methyl-testosterone (methyltestosterone) that is found to resist the hepatic metabolism and cause potentially serious liver toxicity or the by esterification reaction of testosterone using fatty-acid to make the ester-linkage testosterone derivative as intramuscular injections (testosterone enanthate, cypionate, and undecanoate) and for oral (testosterone undecanoate TU only). Although testosterone undecanoate TU is found to be absorbed via the intestinal lymphatic system and has been widely available and used outside the U.S, due to its pharmacokinetic profile it was never approved for use in the U.S. [2]. The delivering of Gels and long-acting testosterone undecanoate 1000mg, both are helping to bring T level to steady state physiological concentration where the long acting intramuscular injections (Testosterone Undecanoate 1000mg for quarterly intramuscular injections, available since November 2004) can reach higher physiological levels, which expressed in more profounder clinical effects and preferable benefits on different organ systems.

The next great innovations, Progresses, Advances in the last two decades are to be categorized in FOUR major innovations on TTh with regards to:

1. Cut off references, 2. Prevention or even remission of type II Diabetes Mellitus, 3. Intermission of treatment (or how long should last TTh?) and 4. Prostate LUTS_Prostate Health, Cancer (paradigm shift). In addition, nine advances in enhancing the role of testosterone as a metabolic hormone with favorable effects on 1. Sexual Function, 2. Obesity, 3. Muscles vs Fats, 4. Bone Health, 5. Blood formulation (Anemia) 6. Cardiovascular effects & blood pressure, 7. Renal Function, 8. Liver function and Steatosis, and 9. Depression The aim of this paper is to throw the light into the four innovations in the following review, hence the advances had been discussed solely or together in many original articles and reviews as an established knowledge so far.

Areas of concentration of 4 Major Innovations

Cut-off or Threshold (Normal Testosterone Range)

Reference ranges are essential for partitioning testosterone levels into low or normal and making the diagnosis of androgen deficiency. Bhasin et al. established reference ranges for Total Testosterone (TT) and Free Testosterone (FT) in a community-based sample of men. These reference ranges generated in a community-based sample of men provide a rational basis for categorizing testosterone levels as low or normal. Men with low TT or FT by these criteria had higher prevalence of physical dysfunction, sexual dysfunction, and diabetes. These reference limits are 12.1-33 nmol/l for total testosterone and 70-141 pg/ml for free testosterone [4].

Prevention or Even Remission of type II Diabetes Mellitus

Type 2 Diabetes Mellitus (T2DM) is often associated with obesity and subnormal serum Testosterone (T) levels. Until recently, there was no indication that men with Type 1 Diabetes Mellitus (T1DM) had subnormal serum T. Studies indicated that, as a rule aged men and men with obesity, about 10% of men with T1DM suffer from hypogonadism. In 2019. Yassin et. al. reported a long-term TRT in men with hypogonadism for eight-year period and found that it completely prevents the progression of prediabetes to overt T2D in men with hypogonadism and prediabetes. TRT also resulted in a marked reduction of Cardiovascular Disease (CVD) risk by reducing body weight, waist circumference, and glycemia and improving dyslipidemia [5]. In 2018, L. Morgunov et. al. studied hypogonadism and its treatment following ischemic stroke in men with type 2 diabetes mellitus. The authors found that TRT is a useful clinical tool to manage ischemic events in this subset of patients whilst having a potentially positive effect in their mobility and the overall quality of life. This study recommended that with careful monitoring, testosterone-deficient patients with T2DM and cardiovascular risk may benefit from TRT [6]. Other observational studies of pooled analyses in obese hypogonadal men with type 2 diabetes found that TRT significantly reduced fasting blood glucose and HbA1c levels, reduced total cholesterol, LDL cholesterol, triglycerides, levels of inflammatory markers and suggesting reduction in the inflammation response and increased HDL cholesterol levels and improved systolic and diastolic blood pressure. TRT of obese, diabetic men improves glycemic control and lipid profiles and may prove useful in reducing the risk of

CVD [7]. These data in references 5,6 and 7 found a validation in the recently published paper in January 2021 in placebo-controlled study over two years [8].

Intermission of Treatment

Four papers discussed this key question on How long should we treatment with testosterone? Our observation indicates that T administration improves body weight and metabolic factors in men with hypogonadism, but withdrawal of T reverses these beneficial effects to appear again when TTh is resumed [9,10]. Two hundred and sixty-two hypogonadal patients (mean age 59.5) received testosterone undecanoate in 12-week intervals for a maximum of 11 years. One hundred and forty-seven men had TRT interrupted for a mean of 16.9 months and resumed thereafter (Group A). The remaining 115 patients were treated continuously (Group B). Prostate volume, Prostate-Specific Antigen (PSA), residual voiding volume, bladder wall thickness, C-Reactive Protein (CRP), Aging Male Symptoms (AMS), International Index of Erectile Function - Erectile Function (IIEF-EF) and International Prostate Symptoms Scores (IPSS) were measured over the study period with anthropometric parameters of obesity, including weight, Body Mass Index (BMI) and waist circumference. Prior to interruption, TRT resulted in improvements in residual voiding volume, bladder wall thickness, CRP, AMS, IIEF-EF, IPSS and obesity parameters while PSA and prostate volume increased. TRT interruption reduced total testosterone to hypogonadal levels in Group A and resulted in worsening of obesity parameters, AMS, IPSS, residual voiding volume and bladder wall thickness, IIEF-EF and PSA while CRP and prostate volume were unchanged until treatment resumed whereby these effects were reversed. These observations indicate that T administration improves body weight and metabolic factors in men with hypogonadism, but withdrawal of T reverses these beneficial effects to appear again when TRT is resumed. TRT interruption results in worsening symptoms. Hypogonadism may require lifelong TRT [11].

Prostate Health and Cancer (Paradigm Shift)

For long time, it was believed that higher testosterone concentrations increased the risk of prostate cancer or caused rapid cancer growth, while low testosterone concentrations would have a protective outcome. PSA is often used as a marker of prostate health, and several studies have investigated this association and at how TRT affects PSA. Most of these studies found that increased testosterone and even for long term does not affect PSA or to be negligible [12-15]. A prostate saturation hypothesis by Morgentaler and Traish put to explain these results, that when androgen receptors on the prostate become “saturated”, the prostate becomes insensitive to further serum testosterone increases, as TRT [16]. A placebo- controlled trial study by Marks found an increase in serum testosterone and DHT when men were on intramuscular TRT for 6 months, however, when biopsied before and after TRT, it showed no change in androgen levels within prostate tissue [17]. PSA is not the perfect marker for prostate cancer; so, several studies have tried to clarify if TRT increases the occurrence of prostate cancer. Plethora studies did not demonstrate testosterone concentrations to be higher in men with prostate cancer comparatively to non-cancer males. Moreover, reports that hypogonadal men with normal PSA did not have lower cancer rates than the general healthy population [18]. Haider et. al. reported the observations of 3 registries on the incidence of Prostate Cancer in Hypogonadal Men Receiving TRT of total of 1023 men followed up for 5 years. The authors suggest that TRT does not increase the risk of PCa. [19] Yassin et. al showed that TRT does not increase the risk for prostate cancer when compared to healthy men and recommended further investigations to truly understand the complex relationship between prostate cancer and testosterone [20]. Other studies were investigated on the effects of TRT on patients who have prostate cancer, especially those who have been diagnosed with prostate cancer, but untreated with prostate cancer. A Prospective data study on 553 patients who underwent prostate biopsy to investigate the role of Testosterone therapy (TRT) in prostate safety and cancer progression. The authors found that the incidence of positive prostate biopsies was lowest in hypogonadal men receiving TRT and lower severity of PCa in terms of staging. These results suggest that TRT might have a protective effect against high-grade PCa [21,22]. In fact, several authors found no recurrences while on TRT, suggesting that TRT can be safe regardless of risk [20,21,23,24]. On the other hand, many studies discussed and examined the influence of testosterone administration on symptom scores of Lower Urinary Tract Symptoms (LUTS) and on benign prostate hyperplasia (BPH) and Lower Urinary Tract Symptoms (LUTS). In a review of Yassin et al. 2006, authors referred to some studies investigating IPSS) the effects of normalizing testosterone levels in elderly men have found a positive effect on variables of the metabolic syndrome and, simultaneously, on scores of the International Prostate Symptoms Score (which is worthy of further investigation in randomized, controlled and sufficiently powered clinical trials [25]. Other studies followed, stating the relationship between erectile dysfunction and LUTS and TTh alone or in combination with Alpha Blockers or PDE-5 inhibitors can improve both ED and LUTS [26]. Studies on interruption of TTh and resumption showed clearly the benefits on LUTS and voiding symptoms, where authors stated that interruption reduced total testosterone to hypogonadal levels resulting worsening of obesity parameters, AMS, IPSS, residual voiding volume and bladder wall thickness, IIEF-EF and PSA while CRP and prostate volume were unchanged until treatment resumed whereby these effects were reversed. TTh interruption results in worsening symptoms. Hypogonadism may require lifelong TTh [8-10].

The traditional assumption that the prostate is an exquisitely sensitive organ to androgen action still holds true, but there are several new insights:

- The saturation model: with lower-than-normal circulating levels of testosterone, all androgen receptors are saturated and a further increase in circulating levels of testosterone has no effect on the prostate.

- This has relevance for prostate disease (prostate cancer and BPH) usually occurring at an age when circulating levels of testosterone are declining. These diseases cannot be attributed to an excess of testosterone.

- It is customary now not to attribute the bother elderly men experience with micturition to the prostate only, but to subsume this under pathology of the lower urinary tract. Surprisingly, these structures have androgen receptors and for their functioning they depend on Nitric Oxide (NO) for the relaxation of smooth muscle structures, having this in common with the biological substrate of erectile function. This explains why PDE5 inhibitors benefit both erectile function and LUTS [26- 29].

Testosterone augments the action of NO and therefore might be helpful in men with LUTS who testosterone is deficient. It becomes apparent that testosterone is not only significant for the formation of male urogenital anatomical structure prenatally, their growth and functioning at the time of puberty but that these structures also need testosterone for maintaining their normal functioning. TTH might improve irritative and obstructive symptoms independent from prostate size [29].

Increased hematocrit is not risky

In a paper came recently from Yassin et al., authors reported very interesting data could define a new paradigm shift in testosterone treatment. Their data suggested that Hematocrit Increase, could reduce death in hypogonadal men under oong term TTh, this can show the implications of Testosterone Therapy (TTh) on Anemia and Complete Blood Count and Paradigm Shift of its Risk Factor (30).

Conclusion

Testosterone deficiency is associated with adverse effects on body composition, bone density, sexual function, and mood and may also increase Insulin resistance, fatty liver and cardiovascular risk factors deterioration. Numerous studies have demonstrated the benefits of TTh overtly hypogonadal men. There are several possible administration routes for testosterone treatment. Each approach has advantages and drawbacks, and the choice of the method of replacement will often be determined by patient preference or co medication (no im injections in patient under Cumarin or similar anticoagulants. Although new developments are promising, it seems that, among the available treatments, only transdermal gels delivery and long-acting injectable TU have provided pharmacokinetic behavior that is giving steady state level within physiological range. Hypogonadism or testosterone deficiency is a significant medical concern or systemic disease that could impact on multiple organ systems causing morbidities and negatively affecting in overall quality of life and associated with increased incidence of sexual dysfunction, metabolic syndrome, diabetes, obesity, depression and others. Due two the above-mentioned advantages, TTh had clearly gained popularity among hypogonadal males as safe and beneficial treatment, with increasing evidence of favorable effects on multi organ systems. Combination therapy with testosterone and other treatments, such as PDE5 inhibitors, is advantageous in some cases and is valuable for patients with hypogonadism who failed PDE5 inhibitor therapy alone.

References

1. Saad F, Gooren LJ, Haider A, Yassin A (2007) An exploratory study of the effects of 12-month administration of the novel long-acting testosterone undecanoate on measures of sexual function and the metabolic syndrome. Arch Androl 53: 353-357.

2. Yassin AA, Haffejee M (2007) Testosterone depot injection in male hypogonadism: a critical appraisal. Clinical Interv Aging 2: 577-590.

3. Swerdloff RS, Robert E (2020) Dudley A new oral testosterone undecanoate therapy comes of age for the treatment of hypogonadal men. Ther Adv Urol 12: 1-16.

4. Bhasin S (2011) Reference ranges for testosterone in men generated using liquid chromatography tandem mass spectrometry in a community-based sample of healthy nonobese young men in the Framingham Heart Study and applied to three geographically distinct cohorts. J Clin Endocrinol Metab 96: 2430-2439.

5. Yassin A, Haider A, Haider K, Caliber M, Doros G (2019) TTh in Men with Hypogonadism Prevents Progression from Prediabetes to Type 2 Diabetes: Eight-Year Data from a Registry Study. Cardiovascular and Metabolic Risk 42:1104-1111.

6. Morgunov L, Denisova I, Rozhkova T, Stakhovskaya L, Skvortsova V (2018) Hypogonadism and its treatment following ischemic stroke in men with type 2 diabetes mellitus. Skvortsova (2018): Hypogonadism and its treatment following ischaemic stroke in men with type 2 diabetes mellitus, The Aging Male 23: 71-80.

7. Haider A, Yassin A, Doros G, Saad F (2014) Effects of Long-Term TTh on Patients with ‘‘Diabesity’’: Results of Observational Studies of Pooled Analyses in Obese Hypogonadal Men with Type 2 Diabetes. Int. J. Endocrinol 2014: 683515.

8. Wittert G, Bracken K, Robledo KP, Grossmann M, Yeap BB (2021) Testosterone treatment to prevent or revert type 2 diabetes in men enrolled in a lifestyle program (T4DM): a randomized, double-blind, placebo-controlled, 2-year, phase 3b trial. Lancet Diabetes Endocrinol 9: 32-45.

9. Yassin A, Nettleship JE, Talib RA, Almehmadi Y, Doros G (2016) Effects of testosterone replacement therapy withdrawal and re-treatment in hypogonadal elderly men upon obesity, voiding function and prostate safety parameters. Aging Male 19: 64-69.

10. Saad F, Yassin A, Almehmadi Y, Doros G, Gooren L (2015) Effects of long-term testosterone replacement therapy, with a temporary intermission, on glycemic control of nine hypogonadal men with type 1 diabetes mellitus – a series of case reports. Aging Male 18: 164-168.

11. Yassin A, Almehmadi Y, Saad F, Doros G, Gooren L (2016) Effects of intermission and resumption of long-term testosterone replacement therapy on body weight and metabolic parameters in hypogonadal in middle-aged and elderly men. Clin Endocrinol (Oxf) 84: 107-114.

12. Raynaud JP, Gardette J, Rollet J, Legros JJ (2013) Prostate-specific antigen (PSA) concentrations in hypogonadal men during 6 years of transdermal testosterone treatment. BJU Int 111: 880-890.

13. Khera M, Bhattacharya RK, Blick G, Kushner H, Nguyen D (2011) Changes in prostate specific antigen in hypogonadal men after 12 months of Testosterone therapy: support for the prostate saturation theory. J Urol 186: 1005-1011.

14. Ho CC, Tong SF, Low WY, Ng CJ, Khoo EM (2012) A randomized, double-blind, placebo-controlled trial on the effect of long-acting testosterone treatment as assessed by the Aging Male Symptoms scale. BJU Int 110: 260-265.

15. Kaufman JM, MillerMG, Garwin JL, Fitzpatrick S, McWhirter C (2011) Efficacy and safety study of 1.62% testosterone gel for the treatment of hypogonadal men. J Sex Med 8: 2079-2089.

16. Morgentaler A, Traish AM (2009) Shifting the paradigm of testosterone and prostate cancer: the saturation model and the limits of androgen-dependent growth. Eur Urol 55: 310-320.

17. Marks LS, Mazer NA, Mostaghel E, Hess DL, Dorey FJ (2006) Effect of Testosterone therapy on prostate tissue in men with late-onset hypogonadism: a randomized controlled trial. JAMA 296: 2351-2361.

18. Morgentaler A, Bruning C, DeWolf W (1996) Occult prostate cancer in men with low serum testosterone levels. Jama 276: 1904-1906.

19. Haider A, Zitzmann M, Doros G, Isbarn H, Hammerer P (2015) Incidence of prostate cancer in hypogonadal men receiving testosterone therapy: observations from 5-year median follow up of 3 registries. J Urol 193: 80-86.

20. Yassin A, AlRumaihi K, Alzubaidi R, Alkadhi S, Al Ansari A (2018) Testosterone, Testosterone Therapy and prostate cancer. The Aging Male 22: 219-227.

21. Yassin A, Salman M, Talib R, Yassin D (2017) Is there a protective role of testosterone against high-grade prostate cancer? Incidence and severity of prostate cancer in 553 patients who underwent prostate biopsy: a prospective data register, The Aging Male 20: 125-133.

22. Pastuszak AW, Rodriguez KM, Nguyen TM, Khera M (2016) Testosterone therapy and prostate cancer. Transl Androl Urol 5: 909-920.

23. Morgentaler A, Rhoden EL (2006) Prevalence of prostate cancer among hypogonadal men with prostate-specific antigen levels of 4.0 ng/mL or less. Urology 68: 1263-1267.

24. Morgentaler A, Caliber M (2019) Safety of testosterone therapy in men with prostate cancer. Expert Opin Drug Saf 18: 1065-1076.

25. Yassin A, El-Sakka AI, Saad F, Gooren LJ (2008) Lower urinary-tract symptoms and testosterone in elderly men. World J Urol 26: 359-364.

26. Yassin A, Saad F, Hoesl CE, Traish AM, Hammadeh M (2006) Alpha-adrenoceptors are a common denominator in the pathophysiology of erectile function and BPH/LUTS – implications for clinical practice. Andrologia 38: 1-12.

27. Vignozzi L, Morelli A (2012) Testosterone protects from metabolic syndrome-associated prostate inflammation: an experimental study in rabbit. J Endocrinol 212: 71-84.

28. Saad F, Yassin AA, Haider A, Gooren L (2011) Effects of testosterone on the lower urinary tract go beyond the prostate: New insights, new treatment options. Arab J Urol 9: 147-152.

29. Yassin A, Alrumaihi K, Talib R, Alkadhi S, Al Ansari A (2019) 186 Voiding function improves under long-term treatment with testosterone undecanoate injections (TU) in hypogonadal men for up to 14 years independent of prostate size. Eur Urol. Suppl 18: e253.

30. Yassin, et.al., (2025). Hematocrit Increase, Reduced Death in Hypogonadal Men: Implications of Testosterone Therapy (TTh) on Anemia and Complete Blood Count and Paradigm Shift of its Risk Factor. Archives of Urology and Nephrology. 4(1); DOI: 10.58489/2836-5828/009