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Review

Oral Testosterone the Undecanoate Formulations for Testosterone Replacement Therapy

Béla E. Tóth1, László Horváth1, Miklós Vecsernyés1*

[1]Affiliation 1: Department of Pharmaceutical Surveillance and Economics, Faculty of Pharmacy, University of Debrecen, Hungary

*Correspondence: vecsernyes.miklos@pharm.unideb.hu

Abstract

Male hypogonadism, or Testosterone Deficiency (TD), involves decreased testicular function, leading to low androgen levels and impaired sperm production. This condition can negatively impact quality of life and increase cardiovascular risks. The adult hypogonadism frequently occurs over 40 in men, and it is characterized by persistent symptoms alongside low testosterone levels, typically below 300 ng/dL. Supplementation with testosterone as a replacement therapy (TRT) is hormonal enhancement found to be effective; however, the delivery methods vary, each with specific advantages and drawbacks. The TRT has potentially life-changing effects, patients feel improved quality of life in several aspects: more energy and muscular strength, increased libido, improved mood, etc. as the most frequent reported outcome.

Oral TRT, particularly testosterone undecanoate (TU), offers notable convenience. TU is absorbed via the lymphatic system, bypassing first-pass hepatic metabolism, making it a promising agent for TRT. Its absorption, however, is influenced by dietary factors, such as lipid intake, thus the high-fat consumption promoting lymphatic absorption. Pharmaceutical technology developed TU formulations incorporate special self-emulsifying systems that enhance lymphatic absorption regardless of food fat content. This lymphatic absorption allows for stable testosterone levels, positioning TU as a viable also for an oral treatment option.

Keywords: testosterone, oral therapy, replacement

1. Introduction

Hypogonadism in men, is divided into primary hypogonadism which is the abnormality of the testis function, and secondary hypogonadism, due to a pituitary or hypothalamic dysfunction which fails to signal the testes. The clinical features of Testosterone Deficiency (TD) depend upon the age of onset, the severity of decreased testicular function, resulting in reduced level of androgens and/or impairment concerned sperm production[1]. It can negatively impact multiple organ systems and diminish quality of life (QoL). The late-onset hypogonadism (LOH) is a clinical syndrome observed in aging men, defined by the presence of persistent specific symptoms and clinical signs, resulted in increased risks of cardiovascular disease, dyslipidemia, obesity, and diabetes alongside biochemical evidence of testosterone (T) deficiency as low serum levels <300 ng/dL (≈10 nmol/L).

The incidence of hypogonadism is ≈12 cases per 1,000 individuals per year. . Clinicians should carefully weigh the anticipated benefits and risks of testosterone replacement therapy (TRT). TRT offers a range of delivery methods, including transdermal gels and lotions, intramuscular and subcutaneous injections, surgically implanted pellets, dermal patches, intranasal gels, and orally administered capsules or tablets. Each route has specific drawbacks recognized by healthcare practitioners and patients—for example, injection pain, dermal irritation, procedures of implantation or risk of liver toxicity.

Oral testosterone is regarded as an attractive option for hypogonadal men due to its convenient route of delivery and patient-driven choice relative to alternative testosterone supplementation modalities. Oral T historically has demonstrated limited efficacy in androgen deficiency, due to extensive first-pass metabolism. This challenge can be addressed by chemically modifying testosterone at the C-17 position to create resistant analogues—such as 17- methyltestosterone—first synthesized in 1935 and used clinically by Ruzicka. Nonetheless, the clinical use of 17-alpha alkylated testosterone formulations is limited due to significant hepatotoxicity[3,4,].

Currently, only the testosterone undecanoate (TU) is the only well-established oral T preparation which is supported by clinical data. It is a highly lipophilic ester that preferentially absorbed via the intestinal lymphatic system, bypassing hepatic first-pass metabolism. Unlike other T esters, which are mainly absorbed and passed

through the portal system, the absorption and systemic availability of TU result from hydrolysis of the ester in systemic circulation, releasing active T. However, TU administration in clinical practice is expected to provide consistently sufficient serum T levels in all hypogonadal men[5,6].

2. Lymphatetic pathway for absorption

The first pass effect of the liver is eliminated if the lipophilic drug directly absorbed through the lymphatic system of the GI tract. Mainly the chylomicrons (CMs) ensure the efficient transfer via lymphatic routes.

Two major pathways exist for CMs absorption: via enterocytes or by the specialized epithelial m cells (i.e. microfold cells) in follicle-associated epithelium (FAE) at Peyer's patches[7].

CMs are lipoprotein particles containing primarily lipids and proteins. Lipids are mostly triglyceride, cholesterol esters in cores, and phospholipids, cholesterol are connected to special proteins in the surface of the CMs. CMs pass through the fenestrations, called lacteals. The type of lipids (such as length of carbon chain and levels of saturation) is one important factor that influence the CM transport. Lipophilicity increases with fatty acid chain length, promoting association with chylomicrons (CM). Medium- to long-chain fatty acids preferentially utilize lymphatic absorption. Upon entry into the mesenteric lymphatics, it can bypass the portal venous system and drain directly into the systemic venous circulation. Consequently, xenobiotics transported via the lymphatic route circumvent first-pass hepatic metabolism[8].

Lymphatic drug delivery systems offer an alternative approach, particularly for drugs with poor stability, low hydrophilicity, and unstable permeability in the GI tract. Their specific Quality by Design (QbD) framework helps ensure efficient lymphatic absorption.

On the other hand, the fat content of food can affect lymphatic transport and thus the drug's bioavailability. A lipid-rich meal induces the secretion of bile acids, which form micelles that promote the absorption of the drug through the lymphatic system. This is an effective way to increase the oral bioavailability of lipophilic drugs[9].

3. Testosterone undecanoate (TU)

Oral administration of TU for the TRT, was introduced over four-decades ago as a therapy. TU is mainly absorbed into the lymph system delivered blood circulation, and the bypassing the liver. TU is de-esterified in the passage thru the intestinal wall and in later on in peripheral circulation[10]. In thoracic lymph duct-cannulated dogs it has confirmed that around 80% of the applied T is available from the systemic hydrolysis of the lymphatically transported TU provide a stable T blood level in the circulation. Otherwise, the total oral bioavailability of TU is low and estimated to be around 7%[11].

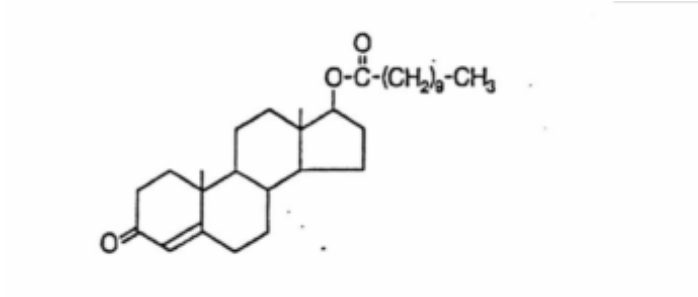

Figure 1.: Structure of testosterone undecanoate

In spite of these facts, the orally applied long-chain ester TU possesses enhanced lymphatic transport and reduced liver metabolism is a good candidate for clinical treatment of TRT. Treated orally with TU preparation of hypogonadal men resulted that the average serum T levels will be in a sufficient therapeutic range and it met the European Regulatory requirements[12].

The orally applied TU dosage form has been marketed for use in Europe was Andriol® till the beginning of 2020 was available in more than 80 countries around the world (not in USA). Andriol® capsule composes of 40 mg of TU (equivalent to 25.3 mg testosterone) in hydrogenated castor oil and propylene glycol monolaurate.

120– 160 mg TU (3-4 capsules of 40 mg) per day are recommended to cover the daily T supplementation. The normal serum T level for young eugonadal men is generally accepted to be approximately 10.4-34.6 nmol/L, which physiological testosterone levels (mean and range) decrease with increasing age. After 3 days of lead-in dosing, a steady state similar to physiological serum testosterone levels is

reached, which provides stable T concentrations during the whole day with a maintenance dosage (40 - 120 mg daily)[13].

4. Highlights of PK characteristics of a TU formulation

The orally administered TU is absorbed from the GI tract via the lymphatic system. It should be underlined that TU is co-absorbed with the fatty meal from the intestine into the lymphatic system. Administration of radioactively labelled TU the peak levels of radioactive TU detected both in the lymph and plasma 2.5-5 hours after administration. TU undergoes hydrolysis to testosterone in the enteric mucosa, after which the liberated hormone circulates in plasma and tissues and is metabolized by the conventional pharmacokinetic pathways[13]. The testosterone levels reached a peak approximately 4-5 hours after ingestion, returning to basal levels after about 10 hours. Approximately 40% of the applied dose was excreted by the kidney in 24 hours[14].

Repeat dosing of TU 2x200 mg/die for 28 days resulted in levels slightly above the lower limit of the normal reference range remained in 75% of subjects in 10-12 hours postdose, indicating some evidence of drug accumulation. The dose of 2x300 mg twice a day, resulted in average serum T about 1.5-fold higher than with 400 mg dose/day, demonstrating a linear dose-proportionality of oral TU[15]. With the dose of 2x100 mg, only 30% of patients reached the normal range.

5. Weakness of the TRT by oral TU / The effect of food on bioavailability

The absorption of lipophilic compounds via the lymphatic route is highly influenced by nutritional habits: high-fat intake promotes lymphatic absorption, thereby increasing the bioavailability of TU. Consequently, variations in dietary composition can lead to significant fluctuations in serum T levels—up to tenfold differences. Meals containing some lipids in food enhances the absorption and result in better bioavailability of testosterone.

Despite the initial favourable results with Andriol, the subsequent major concerns should be concluded during the drug therapy.

- First, the diurnal fluctuations cause serum testosterone to rise briefly toward the normal range after intake, but levels subsequently fall back to hypogonadal values. This means that, on average, serum testosterone does not reach physiologic levels, and most patients receiving treatment remain hypogonadal.
- Second, the absorption of Andriol® and Andriol Testocaps® oral capsules has been demonstrated to be greatly affected a patient's eating habits and dietary patterns.

To evaluate the impact of food on TU bioavailability, a study was conducted using Andriol Testocaps[16]. TU were given orally either while fasting or following consumption of a standard continental breakfast. PK parameters were calculated. When administered after an overnight fast, serum levels of TU and T were low, often below the limit of quantification, indicating minimal absorption in the fasting state. Conversely, taking Andriol Testocaps with food resulted in improved bioavailability, likely due to increased formation of chylomicrons in response to the lipid load from the meal and/or enhanced solubilization of the compound within the intestinal tract during digestion. Additionally, delayed gastric emptying may also contribute to this effect[11].

The oral applications of TU demonstrate a good tolerability with improved T levels [3,17]. However, high intra- and interindividual variability observed in serum T levels following oral TU treatment is, at least in part, attributable to differences in dietary intake and timing of administration.

6. Clinical observations

Testosterone deficiency and LOH may adversely affect multiple organ functions and quality of life (QoL) included reduced erectile function in 88% and 'libido' is decreased in 83% of subjects before treatment[18].

Treatment consisted of daily administration of 120 mg/day testosterone undecanoate Andriol® given orally for no less than 2 months in hypogonadism. produced restoration of plasma testosterone levels in all patients[13].

TRT studies in aging men have shown positive effects on body composition, parameters such as visceral fat mass, height, velocity, increases of haematocrit and haemoglobin insulin resistance and the symptom complex related to partial androgen deficiency by the aging and longer survival or improved quality of life[19]. without significant hepatotoxicity, or worsening hypertension in hypogonadal men [3,17],[16,20,] no

change in PSA or size of prostate [24,22]. On the other hand, the treatment with oral TU also improved subjective depressive symptoms [18]. The TU treatment with 120 mg/day doses slightly improved some semen parameters, but he results were not convincing [16] but the higher 240 mg/day TU doses increased sperm concentration.

RCT trials demonstrated significant improvements also in QoL scores, sexual interest and behaviour[,21]. Only a few mild to moderate adverse events were reported these, such as headache and gastrointestinal complaints[17].

A long- term 10-year follow-up study of study suggested that TRT with oral TU in a clinically effective dose of 80-240 mg/day is a safe and well tolerated. The safety concerns of long-term safety on potential hepatoxic effects were then rejected, since no alteration in the biochemical parameters of liver function or no increased hepatic enzymatic breakdown of the androgen over time could be detected in these patients[6,23].

7. Regulatory and marketing status

TU which is lipophilic long-chain ester preserves the androgenic activity that has been attributed to formation of T via systemic hydrolysis of lymphatically transported TU.

The TU as a prodrug formulation, was selected for TRT because it is specific characteristics: highly lipophilic and is manly absorbed via intestinal lymphatics bypassing hepatic metabolism in contrast with other T formulations, such as esters, which are less lipophilic and mainly absorbed via the portal system. and these latter are ineffective in the treatment of male androgen deficiency syndromes due to extensive first-pass metabolism in liver, which otherwise also raises safety concerns. (TU), which is intended to enhance delivery bioavailability via intestinal lymphatics. Andriol® and Andriol Testocaps® were marketed in more than 80 countries.

Furthermore, it is unlikely that treatment of hypogonadal men with this TU formulation would yield average serum T levels in real life conditions in a majority of men to meet the current regulatory and clinical scrutiny.

Due to the low bioavailability and the uncertain absorption process, the oral formulation of Andriol® and Andriol Testocaps® did not meet the stated regulatory standards for safety and efficacy, (i.e. on avg. serum T concentrations for at least 75% of treated men and the C_{max} peak T below 1500 ng/dL) the FDA (USA) refused granting

the Marketing Authorization thus did not allow the distribution in the USA. In Europe, with strict endocrinological control the oral TU used for TRT. However, in the beginning of 2020 it was removed (e.g. in Hungary) from the therapeutic protocol.

In the USA, there had been a broad search for novel oral drug delivery system that could offer required therapeutic concentrations independent of ingestion a rich-fat meal. Based on specific properties of the self-emulsifying drug delivery system (SEDDS) JATENZO and TLANDO utilizes for lymphatic uptake of TU with safe therapeutic effects without evidence of liver dysfunction. The SEDDS described herein integrates a high-HLB surfactant, a co-surfactant, and a TU-dissolving carrier oil. In brief within the GI tract, self-emulsification occurs, enlarging the interfacial area and the lipophobic environment promoting the enhanced absorption of TU [26].

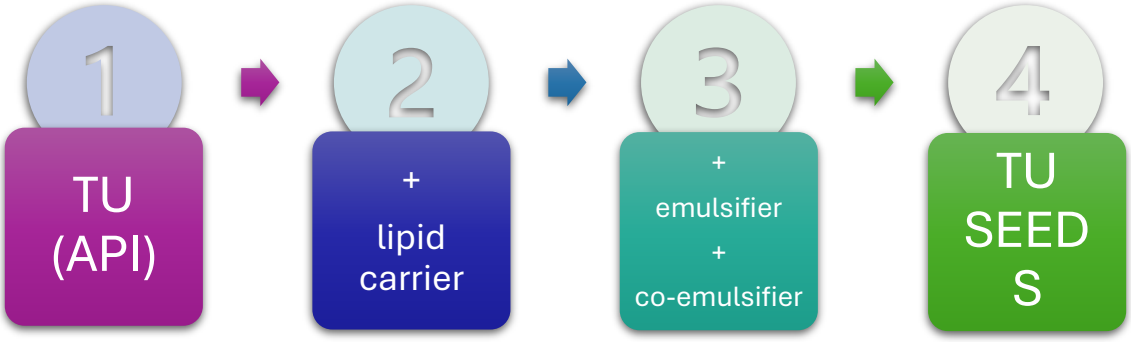

Figure 2.: Steps for a self-emulsifying drug delivery systems (SEDDS) is a proven method for poorly soluble substances by increasing the solubility and bioavailability. SEDDS containing higher percentages of solubilizers and/or surfactants. The formulation in KYZATREX: DL-alpha-tocopheryl acetate (Vitamin E), phytosterol esters, polyoxyl 40 hydrogenated castor oil and propylene glycol monolaurate; JATENZO: oleic acid, polyoxyl 40 hydrogenated castor oil, borage seed oil, peppermint oil, and butylated hydroxytoluene; TLANDO: ascorbyl palmitate, glyceryl monolinoleate, polyethylene glycol 8000, polyoxyl 40 hydrogenated castor oil

Lately, the slightly modified oral TU formulations were developed as Jatenzo, Tlando, Kyzatrex and marketed globally (also in the USA). The injectable formulations of TU depot injection (Aveed and Nebido) remain the most cost-effective therapeutic option and these are appropriate for most patients as an initial therapy[25]. Transdermal administration includes gels, liquids and patches since the 80's.

Table 1: Available oral TU formulations (FDA, USA)

	FDA Approval	PharmacoKinetics	Time to T_{max}	Bioavailability in $AUC_{0\text{-}last}$ in nmolh/L	Metabolism	Starting Dose	Titration	Special Precautions	Significant Adverse Effects
Jatenzo	Yes; April 2019	Ester bond is cleaved to release testosterone + inactive undecanoate; testosterone is then broken down to biologically active dihydrotestosterone (DHT) by 5a reductase	5 hours	1034	Beta oxidation	237 mg taken as one 158 mg capsule BID	Up or down titrate to maintain T concentration within normal range	None	Small increased incidence of elevated systolic blood pressure
Andriol	No		4–5 hours	41.7–1050		120–160 mg taken as 1–2 40 mg capsules BID for 2–3 weeks for initial dosing	Up or down titrate for maintenance dose of 40–120 mg daily	Must take with food as bioavailability is highly dependent on fat intake	Minor GI upset and headache
Tlando	Yes; March 2022		4–6 hours	29581		225 mg taken as one 112.5 mg capsule twice daily	No titration; if serum T is outside of normal range (300–1080 ng/dL), discontinue	Must take with food for optimal absorption	Small increased incidence of elevated systolic blood pressure
Kyzatrex	Yes; August 2022		4–5 hours	10425±5521		200 mg twice daily	Up or down titrate based on serum testosterone for a maintenance dose between 100 mg once daily–400 mg twice daily	Must take with food for optimal absorption	Small increased incidence of elevated systolic blood pressure

The latest TU SEDDS dosage form is predicated on the requirement for a high-fat meal to optimize absorption.

- **JATENZO®** (2019; Clarus Therapeutics Inc., USA) obtained FDA approval as the first oral TRT indicated for primary and central hypogonadism. Like other exogenous androgens, JATENZO was designed with a self-emulsifying drug delivery system that integrates hydrophilic and lipophilic components to promote intestinal lymphatic uptake. This formulation enables administration with a standard meal (15–45 g fat) rather than the previously necessary high-fat diet. Following ingestion, serum testosterone rises rapidly, reaching a peak at 2–4 hours and gradually diminishing toward sub-physiologic levels by about 9 hours, which underpins a twice-daily dosing strategy[25].
- **TLANDO®** (2022, Lipocine Inc., USA), another TU oral formulation utilizing SEDDS, has recently been authorized by the FDA for managing of male hypogonadism. This capsule contains 112.5 mg of TU in a unique triglyceride/lipid formulation (with an antioxidant: ascorbyl palmitate). Consistent with all other TU preparations, this lipid emulsification is intended to maximalize the absorption of TU through the intestinal lymphatic system. This formulation was postulated to avoid dose adjustment when employed twice daily for TRT. Since preparation does not require dose titration, regular blood testing simplifying both usage and dosage monitoring[25].

  An open-label trial with TLANDO (225 mg twice daily) for 24 days in hypogonadal men demonstrated stable 24-hour average serum testosterone in

80% of participants without dose adjustment. In a smaller cohort, dietary fat content diets had no effect on bioavailability[25,26].

- **KYZATREX®** (2022, Marius Pharmaceuticals, USA) Unique to Kyzartrex is a TU softgel formulation that includes vitamin E and phytosterols to promote lymphatic absorption while aiming to minimize hepatic exposure. In a clinical trial 88% of male participants maintained mean serum testosterone within the eugonadal range (95% CI 82–93), supporting FDA authorization. The product provides 100 mg, 150 mg, and 200 mg capsules; the recommended starting dose is 200 mg orally twice daily with meals, with subsequent titration after seven days according to serum T levels[25].

In general, matching the right patient with the right TU formulation to ensure good compliance is essential for maintaining long-term satisfaction of TRT, therefore, individualizing therapy is important[26].

8. Conclusion

Treatment options for male hypogonadism, particularly in cases of LOH, as characterized by low serum T levels and associated symptoms and impaired QoL, include various delivery methods. The oral formulations of TU offering notable advantages in convenience and patient preference. However, the efficacy of oral T has traditionally been limited by first-pass hepatic metabolism. Advances in formulation, such as TU, have improved bioavailability through lymphatic absorption, especially when taken with lipid-rich meals. processes. Despite these improvements, variability in dietary habits and individual responses remains a challenge, affected serum T levels and treatment consistency. Newer formulations of TU with castor oil and propylene glycol laurate instead of oleic acid, has similar PK and provide improved storage conditions.

A thorough understanding of these factors is essential for optimizing therapy, ensuring safety, and achieving desired clinical outcomes. It can be concluded that orally administered TU is a valuable tool for TRT. Continued research aims to improve bioavailability in formulation innovations and personalized treatment strategies will further enhance management of hypogonadism to ensure the right plasma testosterone levels, by the availability of various formulations for TRT.

Over the past two decades, testosterone replacement therapy (TRT) prescription rates have risen worldwide, largely driven by claims that testosterone enhances energy and endurance. This increase, however, does not appear to reflect treatment of patients concordant with clinical guidelines. Although other TRT formulations are available, oral TU remains an important option for individual therapy, and the comparisons among different testosterone products underscoring the need for further research to optimize personalized treatment strategies.

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