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Review

Comparative review of the pharmacokinetics and pharmacodynamics of testosterone therapies in type 2 diabetes

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ABSTRACT

The objective of this review is to evaluate how formulation-dependent PK characteristics of oral, transdermal, intramuscular (IM), and subcutaneous testosterone therapies translate to metabolic effects in hypogonadal men with T2D. A narrative review of clinical trials, PK studies, and endocrinology guidelines indexed in PubMed and Scopus up to October 2025. Evidence was synthesized comparing absorption pathways, kinetic variability, androgen receptor (AR) engagement patterns, and downstream metabolic endpoints including insulin sensitivity and glycemic control. Transdermal formulations provide relatively stable, circadian-like testosterone concentrations supporting gradual anabolic effects, whereas oral TU produces short-lived peaks with larger fluctuations that limit sustained anabolic and metabolic signaling. Oral TU utilizes lymphatic transport to reduce first-pass hepatic metabolism, increases free testosterone via hepatic SHBG suppression, yet yields lower total serum testosterone concentrations relative to injectables. Transdermal absorption is highly anatomical site-dependent, with scrotal application significantly enhancing systemic levels and DHT conversion. Short-acting IM esters generate supraphysiological peaks and deep troughs, destabilizing glucose regulation and enhancing aromatase/5α-reductase activity. In contrast, long-acting esters demonstrate flip-flop kinetics with prolonged, stable serum testosterone exposure, enabling continuous AR activation and sustained improvements in insulin sensitivity and glycemic control. Formulation-specific PK dictate hormonal stability and metabolic benefit in hypogonadal men with T2D. Long-acting injectable therapies provide the most favorable and durable endocrine–metabolic profile by maintaining continuous physiologic AR stimulation. In comparison, the more oscillatory exposure produced by transdermal gels, oral TU, and short-acting esters may deliver anabolic benefits yet insufficient hormonal

Abbreviations: ABC, ATP-Binding Cassette; ADME, Absorption, Distribution, Metabolism, and Elimination; AG, Androsterone-Glucuronide; AGP, Alpha-1-Acid Glycoprotein; AMP, Adenosine Triphosphate; AMPK, AMP-Activated Protein Kinase; AUC, Area Under the Curve; BPH, Benign Prostatic Hyperplasia; BMI, Body Mass Index; β-cells, Beta Cells; C, Concentration; Cavg, Average Plasma Concentration; Cmax, Concentration maximum; CBG, Corticosteroid-Binding Globulin; CL, Clearance; CL/F, Apparent Clearance Adjusted for Bioavailability; CV, Cardiovascular; CYP19A1, Aromatase Enzyme; DHT, Dihydrotestosterone; DPG, Dipropylene Glycol; E2, Estradiol; FDA, Food and Drug Administration; Fe, Fraction Excreted Unchanged; FSH, Follicle-Stimulating Hormone; GLUT4, Glucose Transporter Type 4; GI, Gastrointestinal; HbA1c, Glycated Hemoglobin; HPG, Hypothalamic-Pituitary-Gonadal; HPT, Hypothalamic-Pituitary-Testicular; HSA, Human Serum Albumin; IL-6, Interleukin-6; IM, Intramuscular; JCEM, A Journal of Clinical Endocrinology and Metabolism; J, Flux; KA, Absorption Rate Constant; Kp, Permeability Constant; LBM, Lean Body Mass; LH, Luteinising Hormone; MRP2, Multidrug Resistance–Associated Protein 2; MRP3, Multidrug Resistance–Associated Protein 3; OATs, Organic Anion Transporters; OGTT, Oral Glucose Tolerance Test; Oral TU, Oral Testosterone Undecanoate; PD, Pharmacodynamics; PEG, Polyethylene Glycol; PG, Propylene Glycol; PK, Pharmacokinetics; R2, Coefficient of Determination; SC, Subcutaneous; SEDDS, Self-Emulsifying Drug Delivery System; SHBG, Sex Hormone-Binding Globulin; SULT2A1, Sulfotransferase 2A1; TE, Testosterone Enanthate; T, Testosterone; T1/2, Terminal Half-Life; T2D, Type 2 Diabetes; TC, Testosterone Cypionate; TG, Testosterone-Glucuronide; T4DM, Testosterone for the Prevention of Type 2 Diabetes Mellitus Trial; Tmax, Time to Reach Maximum Concentration; TNF-α, Tumor Necrosis Factor Alpha; TRT, Testosterone Replacement Therapy; TU, Testosterone Undecanoate; TS, Testosterone-Sulfate; UGT2B17, UDP-Glucuronosyltransferase 2B17; V/F, Apparent Volume of Distribution Adjusted for Bioavailability; Vd, Volume of Distribution.

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stability for consistent improvements in glycaemic control. These findings reinforce the need to prioritise sustained-release formulations when targeting metabolic endpoints in men with T2D receiving TRT.

1. Introduction

1.1. Epidemiology of type 2 diabetes

Type 2 diabetes (T2D) is an escalating global health crisis. The Global Burden of Disease analysis estimates indicate 561 million people were living with diabetes as of 2023, with cases forecasted to reach 1.3 billion by 2050 [1]. Roughly 43 % of adults with diabetes remain undiagnosed, contributing to an estimated 3.4 million deaths and global healthcare costs exceeding $1.5 trillion AUD worldwide [2]. In Australia, diagnoses increased from 460,000 people in 2000 to approximately 1.3 million people in 2021 [3]. By 2022, diabetes ranked seventh amongst leading causes of death, with 6050 deaths directly attributed and approximately 21,900 deaths (11 %) when other associated factors were included. These figures underscore both the global trajectory and the national health burden [4].

1.2. T2D and hypogonadism

T2D pathophysiology is characterized by insulin resistance in skeletal muscles and liver, progressive β-cell dysfunction, and chronic low-grade inflammation typically driven by visceral adiposity [5]. These metabolic disruptions converge on the hypothalamic-pituitary-gonadal (HPG) axis through hyperinsulinemia, inflammatory cytokines and reduced sex hormone-binding globulin (SHBG) [6]. Low circulating testosterone is an indicator of T2D in many men resulting in male hypogonadism, also known as androgen deficiency [6,7]. Hypogonadism is a condition diagnosed when testosterone serum levels are abnormally low, typically below 10.4 nmol/l (300 ng/dl), which is accompanied by the symptoms of androgen deficiency such as reduced muscle mass, decreased blood glucose uptake and insulin resistance [8].

Epidemiologic data indicate a high prevalence of low testosterone among men with T2D, predominantly with hypogonadotropic patterns [9]. A Journal of Clinical Endocrinology and Metabolism (JCEM) study using equilibrium dialysis to measure free testosterone in men with T2D found that 33 % of the participants had low testosterone [9]. Most cases showed secondary hypogonadism, with non-elevated luteinizing hormone (LH) and follicle-stimulating hormone (FSH) despite low testosterone, indicating reduced hypothalamic–pituitary drive [9]. Importantly, a similar pattern was also observed in T2D men with a normal BMI, suggesting obesity alone isn't indicative of why men with T2D have low testosterone [6]. Other diabetes-related factors, such as insulin resistance, are also likely contributors. A larger cross-sectional cohort of 355 individuals with T2D revealed that 17 % had overt hypogonadism (total testosterone < 8 nmol/l and bioavailable testosterone < 2.5 nmol/l), and a further 14 % met the borderline criteria (total testosterone of 8–12 nmol/l) [9,10]. Importantly, this was not only an older men's issue; in younger men (18–35 years old) with T2D, 33 % had low free testosterone by the standard cutoff of < 220 nmol/l, and 58 % were below age-specific normal ranges [10]. Their gonadotropins, LH/FSH, were normal despite the low testosterone, again pointing to secondary hypogonadism [10]. Multiple studies showcase an inverse relationship between BMI and free/total testosterone and lower SHBG in T2D [11–13]. The presence of biochemical hypogonadism in non-obese men argues for additional metabolic and inflammatory drivers beyond adiposity alone [14]. These population data sets indicate that obesity and T2D together confer a higher prevalence of subnormal testosterone rather than obesity alone, highlighting an additive metabolic effect [10].

2. Aim

Given the global burden of T2D and the high prevalence of hypogonadism among affected men, a mechanistic understanding of how TRT influences metabolic outcomes is clinically significant. This review critically examines how formulation-dependent pharmacokinetics (PK) characteristics shape pharmacodynamic (PD) responses, and in turn, how these factors modulate insulin sensitivity, glycemic control, and body composition in hypogonadal men with T2D.

We evaluate the impact of formulation type, route of administration, and interindividual variability on testosterone exposure and metabolic efficacy, highlighting key PK determinants such as bioavailability, protein binding, and metabolic conversion that underpin therapeutic outcomes and safety. By integrating evidence across oral, transdermal, intramuscular (IM), and subcutaneous (SC) delivery systems, this review elucidates how differences in absorption sites, dosing intervals, and metabolic processing translate into variable clinical responses. Finally, we synthesize data from recent clinical trials to contextualize the relationship between PK profiles, efficacy and metabolic benefit, identifying ongoing knowledge gaps and directions for future research.

3. Methods

A targeted literature search was conducted to comparatively analyze PK and PD profiles of different TRT formulations. This provided the foundation for our comparison of the PK of different testosterone formulations and routes of administration in men with T2D. The preference of Quartile 1 articles was implemented, with research inclusions consisting of human studies, open label, randomized, clinical trials as well as full reviews to solidify background knowledge. The database utilized was PubMed, and hand searching reference lists of included papers using relevant keywords. Appropriate studies were selected and classified *via* formulation status and their relevance to PK and/or PD. Outcomes assessed included PK parameters and T2D outcomes. Formulations identified in the foundations of comparative review were transdermal gels, oral TU, and testosterone injections.

Articles published until October 2025 were included.

4. Testosterone replacement therapy in hypogonadism

Testosterone replacement therapy (TRT) aims to restore androgen exposure in men with diagnosed hypogonadism [15]. According to the FDA, TRT should aim to restore average serum testosterone concentrations within the eugonadal range of 10.4–34.7 nmol/l (300–1000 ng/dl) which is the normal early morning range for males, depending on individual factors such as age. In healthy men, serum testosterone follows a circadian rhythm that peaks in the morning and gradually declines throughout the day, with levels falling by as much as 30 to 40 % by the evening [8,15]. This rhythm reflects hormone release from the hypothalamic-pituitary axis and ensures stable androgenic signaling across target tissue [16]. In practice, TRT may aim to replicate these physiological rhythms rather than simply raising testosterone serum concentrations [16,17]. This targets a eugonadal window where the goal is to achieve a concentration range that restores androgen-dependent functions and monitors both magnitude and temporal patterns of testosterone exposure [18]. Achieving sustained steady delivery of TRT minimizes excessive peaks and troughs that are responsible for side effects such as gynecomastia, fatigue and sudden mood changes, while maintaining consistent anabolic and metabolic effects across treatment duration [19].

The formulations and administration routes of TRT therapies

determine the exposure and, therefore, the effects of said therapies. Dosage forms differ fundamentally in absorption and release kinetics [19]. Across all different treatments absorption, distribution, metabolism, and elimination (ADME) processes determine the key pharmacokinetics parameters (T_{max}, C_{max}, elimination half-life, AUC and peak–trough amplitude), which in turn govern pharmacodynamic responses [20]. In contrast, high SHBG may reduce tissue-level androgen effects despite normal total testosterone [14]. These differences influence key metabolic outcomes such as insulin sensitivity, glucose uptake and body composition [21]. This highlights the importance of selecting formulations and dosing strategies that maintain physiological normal androgen levels to optimize glycemic control and metabolic functions in hypogonadal men with T2D [19,22].

5. Testosterone mechanistic behavior in T2D

Testosterone exerts its metabolic effects primarily through activation of androgen receptors (AR) in skeletal muscle, liver, adipose tissue, and pancreatic β-cells organs central to glucose regulation and insulin sensitivity [22]. As illustrated in Fig. 1, AR stimulation enhances AMP-activated protein kinase (AMPK) and GLUT4 expression in skeletal muscle, facilitating glucose uptake and improving insulin responsiveness [23]. Fig. 2 further explains how within the liver, testosterone suppresses gluconeogenic enzymes such as phosphoenolpyruvate carboxykinase and glucose-6-phosphate, reducing hepatic glucose output [24]. In adipose tissue, physiological androgen exposure inhibits adipocyte differentiation, decreases visceral fat accumulation and downregulates pro-inflammatory cytokines (e.g., TNF-α, IL-6), thereby mitigating insulin resistance [23,24]. Additionally, testosterone supports β-cell survival and insulin secretion via paracrine modulation of pancreatic function. In contrast, androgen deficiency disrupts these processes, promoting visceral adiposity, systemic inflammation, and impaired glucose homeostasis [25]. Collectively, these pathways position testosterone as a key metabolic regulator whose PD actions depend on both receptor engagement and the stability of circulating hormone concentrations across dosage forms [25].

6. Testosterone mechanism of action

Following administration, testosterone circulates primarily bound to SHBG and albumin, while a small amount remains unbound [21]. This free testosterone is biologically capable of entering the target tissue to activate AR's (Fig. 1) [21]. In skeletal muscle, AR activation increases glucose uptake by increasing glucose transporter type 4 (GLUT4) translocation and improving insulin sensitivity [21]. Variation in SHBG concentrations, which are common in men with T2D due to high insulin levels and hepatic insulin resistance, can substantially alter free testosterone availability and thus modulate pharmacodynamic response [12,21]. Specifically, lower SHBG concentration increases the amount of available free bioactive testosterone, improving metabolic responsiveness but also contributes to faster clearance [21,26]. Low testosterone promotes insulin resistance, visceral adiposity, and systemic inflammation by reducing muscle mass and altering adipocytokines [11,27]. Increased visceral fat elevates aromatase activity and inflammatory cytokines, which suppress the HPG axis and reduces Leydig cell testosterone synthesis [28]. Testosterone exerts its effects through both direct receptor activation and conversion to potent metabolites [28]. Upon entering target cells, testosterone binds to intracellular AR, forming a hormone–receptor complex that is translocated to the nucleus and modulates gene transcription of androgen-responsive elements, influencing protein synthesis, cell differentiation, and growth [28,29]. In certain tissues such as the prostate and skin, testosterone is locally converted by 5α-reductase to dihydrotestosterone (DHT), which has greater receptor affinity and drives virilizing effects [30]. In other tissues like muscle and bone, aromatization to estradiol via aromatase contributes to anabolic and skeletal maintenance actions [28].

7. Effects of testosterone on body composition

Testosterone's anabolic effects on muscle and catabolic effects on fat are well studied in both eugonadal ageing men and hypogonadal populations, translating favorably on body composition changes in men with T2D [12]. Restoration of testosterone tends to increase lean body mass (LBM) while reducing fat mass, particularly visceral fat [31]. Clinical trials consistently demonstrate that TRT induces hypertrophy of skeletal muscles [32–34]. For instance, Allan *et al.* (2008) showcased that one year of transdermal testosterone therapy in older men with a mean age of 60 significantly increased fat-free mass and skeletal muscle mass compared to the placebo group [34]. In this study, total LBM rose while age-related thigh muscle loss was essentially prevented by TRT,

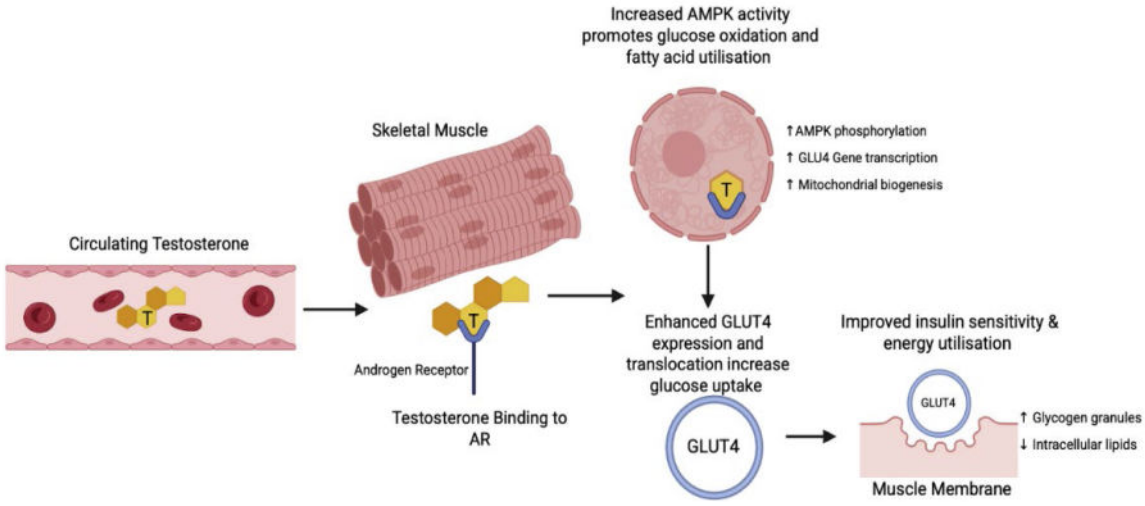

Fig. 1. Mechanistic model of testosterone-mediated regulation of glucose metabolism in skeletal muscle. Circulating testosterone enters skeletal muscle and binds to the intracellular androgen receptor (AR), initiating genomic and non-genomic signaling cascades. AR activation enhances AMP-activated protein kinase (AMPK) phosphorylation, promotes GLUT4 gene transcription and translocation to the sarcolemma, and increases mitochondrial biogenesis. Collectively, these effects augment glucose oxidation and fatty acid utilization, resulting in improved insulin sensitivity, enhanced glucose uptake, and more efficient energy metabolism. Such mechanisms help restore metabolic homeostasis in hypogonadal men and support the insulin-sensitizing effects of testosterone replacement therapy [22–25]. Image created with BioRender (www.biorender.com).

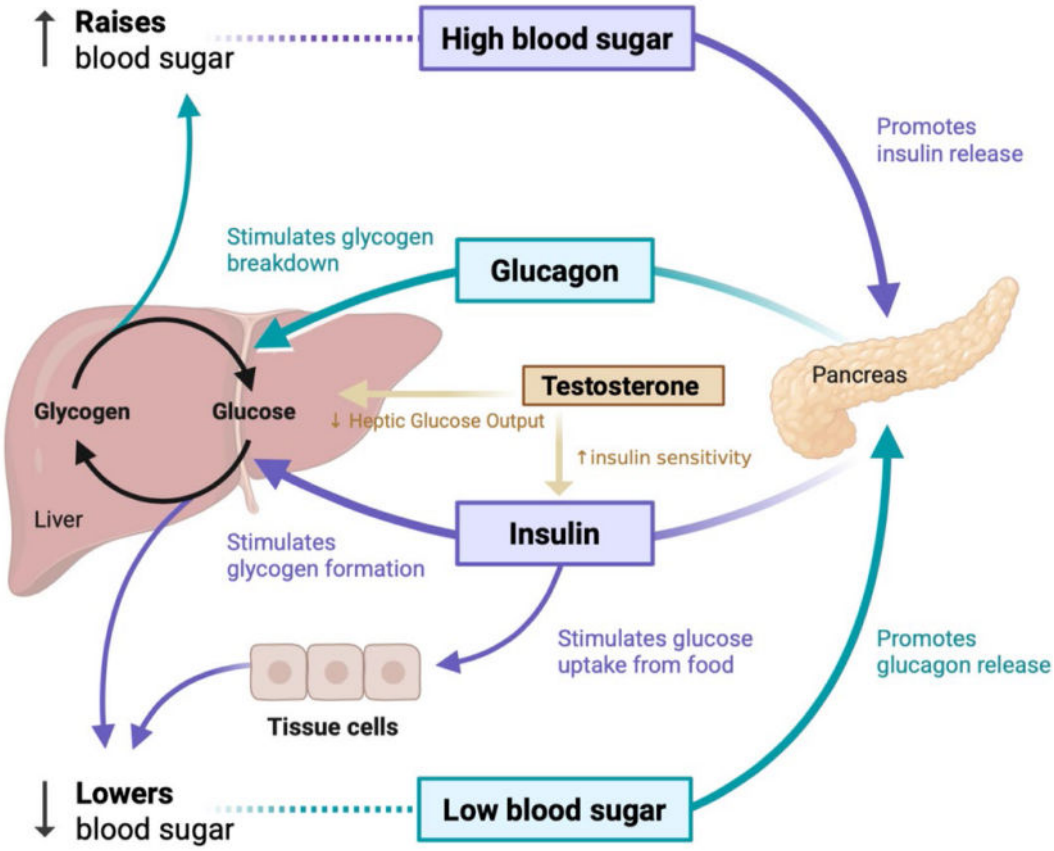

Fig. 2. Testosterone's modulatory role in glucose homeostasis via insulin–glucagon regulation. Schematic representation of hepatic and pancreatic control of blood glucose, highlighting testosterone's effects. Under low blood glucose conditions, pancreatic α-cells release glucagon, which stimulates hepatic glycogen breakdown and glucose release into the bloodstream, increasing plasma glucose levels. Conversely, high blood glucose promotes β-cell insulin secretion, enhancing tissue glucose uptake and glycogen synthesis in the liver, ultimately lowering circulating glucose. Testosterone improves insulin sensitivity in peripheral tissues and reduces hepatic glucose output, thereby shifting glucose balance toward improved glycemic control. These interactions collectively illustrate how testosterone intersects with endocrine pathways involved in metabolic regulation, particularly relevant to hypogonadal men with metabolic dysfunction [22–25]. Image created with BioRender (www.biorender.com).

whereas placebo recipients lost muscle over the 12 months [34]. Testosterone seemed to reduce age-associated visceral adiposity gain, where men on the placebo arm gained significant visceral fat over the year [33]. Those on TRT either saw a decrease in visceral fat or gained no further visceral fat, despite no overall change in total body weight [34]. Importantly, the reduction in visceral adipose tissue correlates with the increase in serum testosterone levels, implicating a direct androgen effect on fat depots [35]. The TIMES2 trial (transdermal gel for 12 months) reported a significant decrease in body fat percentage in the testosterone group of approximately 0.9 % body fat at 12 months vs baseline ($P < 0.05$), along with a reduction in waist circumference of 1.6 cm or more [32]. This is further seen in the BLAST study of men with T2D, where 30 weeks of testosterone undecanoate injections led to a significant reduction in waist circumference, weight and BMI compared

Table 1
Pharmacokinetic comparison of different testosterone dosage forms.

Formulation	Dose	T_{max}	C_{max} (nmol/l)	C_{avg24} (nmol/l)	CL/F (l/hr)	V_d (klL)	$T_{½}$	References
Transdermal gel Androgel®	1 % 50mg	4hr	29.3 ± 1.9	19.2 ± 1.1	49.44	-	15.2hr	40,105
Transdermal gel Androgel®	1.62 % 20.25–81mg	8hr	29 ± 16.6	19.2 ± 1.1	-	-	14.6hr	106
Oral TU Jatenzo®	158–396 mg twice daily	2hr	34.9 ± 20.1	14.0 ± 4.4	-	-	29hr	55,68
IM TE	100mg/week	24.1hr	30 ± 8.3	19.8 ± 4.4	50.6	13.8	7 days	67,85
IM TC	200mg/ 2 weeks	4–5 days	38.6 ± 10.3	-	108	12.4–14.4	8 days	40,77
IM TU Reandron®	1000mg	7 days	42	-	198	12.2	53 days	40,63,72
SC TE	100mg/week	24.1hr	30.06 ± 8.28	19.83 ± 4.41	60.8	23.8	10 days	67,72,85
SC TU Reandron®	1000mg	8 days	29.15	-	-	-	-	72

Abbreviations: Maximum concentration (C_{max}), Time to reach maximum concentration (T_{max}), apparent clearance (CL/F), Volume distribution (V_d) Terminal half-life ($t_{½}$), Intramuscular (IM), Subcutaneous (SC), testosterone enanthate (TE), testosterone cypionate (TC), Testosterone undecenoate (TU) Note: Oral TU values represent fed-state administration. CL values assuming an 80kg.

to placebo [36].

8. Pharmacokinetic comparison of different formulations of testosterone

In this section, we provide a comparative overview of the PK characteristics of clinically used testosterone replacement formulations. It outlines how routes of administration influence key parameters such as C_{max}, C_{avg}, T_{max} and bioavailability.

Several studies have presented comparative pharmacokinetic data for three main testosterone formulations: oral, topical/transdermal and injection. These can be seen in Table 1.

8.1. Absorption

The absorption of testosterone is highly dependent on the formulation, route of administration, excipient design, and patient-related factors, all of which influence key pharmacokinetic parameters such as C_{max}, C_{avg}, T_{max} and bioavailability [19]. Table 1 and Figs. 3–5 summarize the comparative absorption characteristics and PK parameters of major testosterone formulations.

8.1.1. Trandermal systems

Testosterone is a lipophilic steroid [28]. Its rate limiting step in transdermal delivery is the crossing of the stratum corneum [37]. After application, the stratum corneum functions as a drug reservoir, and the drug is released gradually into systemic circulation (Fig. 3) [38]. We can assume flip-flop kinetics ($k_a < k_{el}$) which produces a relatively smooth concentration-time curve, and prolonged half-life with significant variability across application sites [39]. Androgel® is a transdermal gel which is available in concentrations of 1.0 % and 1.62 %, containing 2.5 g or 5.0 g of gel, equivalent to 25 or 50 mg of testosterone, respectively [40]. The skin permeation rate of testosterone gel in vitro followed a linear absorption model, and testosterone began permeating skin within minutes, reaching a transdermal steady-state flux around 60–90 min [41]. However, the elimination half-life of the testosterone once it's in the bloodstream is longer, typically 8–22 hours due to its flip-flop effect [40].

A study conducted by Miller *et al.* (2011) demonstrated that application of a 1.62 % testosterone gel to the shoulders or upper arms resulted in 30–40 % higher bioavailability compared to abdominal application, highlighting the significant impact of anatomical site on transdermal absorption [42]. Furthermore, application to the scrotal skin resulted in significantly greater absorption [43]. A study by Iyer *et al.* (2017) demonstrated that applying a 12.5 mg dose of testosterone cream to the scrotum produced an eightfold increase in bioavailability (C_{max} ~16.3 nmol/l), whereas a substantially higher 100 mg dose applied to the abdomen was required to achieve comparable systemic concentrations [43].

This site-dependent variability in transdermal absorption can potentially be explained by Ficks first law of diffusion ($J = K_p$ x C) [44]. Here, flux (J) is determined by the permeability constant (k_p) and the concentration gradient (c) across the skin. Since the scrotal dermis is characterized by exceptionally high vascularity and an unusually thin stratum corneum, we can assume that K_p is elevated, facilitating passive diffusion along the concentration gradient [45,46]. In addition, genital skin expresses elevated cutaneous 5α-reductase activity, leading to greater local conversion of testosterone to DHT, contributing to increased systemic androgen exposure compared with non-scrotal application sites [47,48]. Moreover, differences in stratum corneum thickness, lipid composition, and barrier integrity between individuals and anatomical sites can significantly alter percutaneous flux [46].

Notably, despite reliable attainment of eugonadal concentrations, transdermal delivery is limited by high inter- and intra-patient variability which is influenced by physiological and physicochemical skin properties [37]. Skin hydration has been shown to enhance permeability by swelling corneocytes and increasing aqueous pathways, a well-established mechanism in the broader transdermal literature, though direct evidence in testosterone delivery is limited [49]. Additionally, local temperature and skin perfusion which may increase with exercise, friction, or environmental exposure can augment dermal clearance and enhance net systemic uptake for transdermal applications [50].

The composition of transdermal formulations exerts a decisive influence on testosterone absorption. Vehicle polarity, solvent strength, and co-enhancer ratios can determine the extent and reproducibility of drug permeation. Permeation enhancers act primarily by altering stratum corneum lipid packing, increasing solvent partitioning, and facilitating diffusion of lipophilic actives such as testosterone [51,52]. In the study by Patel et al. (2021), quantitative confocal Raman spectroscopy and in vitro permeation testing revealed that the rate and extent of drug (and solvent) delivery are tightly linked [53]. Vehicles with greater skin uptake correlate with higher drug flux (R^2 ~0.95) confirming that formulation achieving higher solvent penetration yields proportionally greater dermal transport. In their study, glycol-based systems, propylene glycol (PG) and dipropylene glycol (DPG), outperformed polyethylene

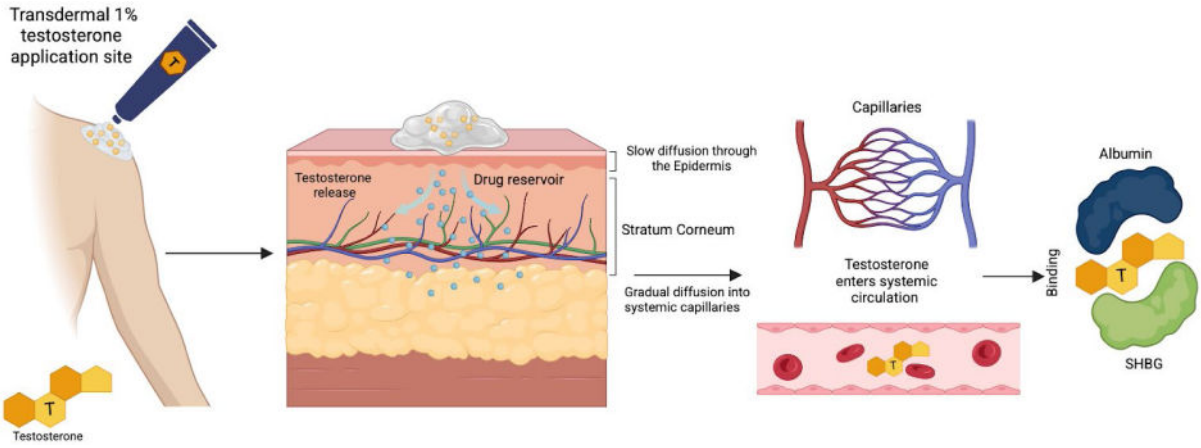

Fig. 3. Transdermal absorption pathway of testosterone gel. After topical application, testosterone forms a cutaneous drug reservoir in the stratum corneum. The drug gradually diffuses through the stratum corneum and epidermis, with absorption limited by skin permeability. Testosterone then enters the systemic circulation via cutaneous capillaries, where it binds to albumin and sex hormone-binding globulin (SHBG) to regulate free hormone availability. The sustained, diffusion-controlled input supports a diurnal-like kinetic profile but is sensitive to factors such as skin thickness, hydration, and enzymatic activity at the application site [37–38]. Image created in BioRender (www.biorender.com).

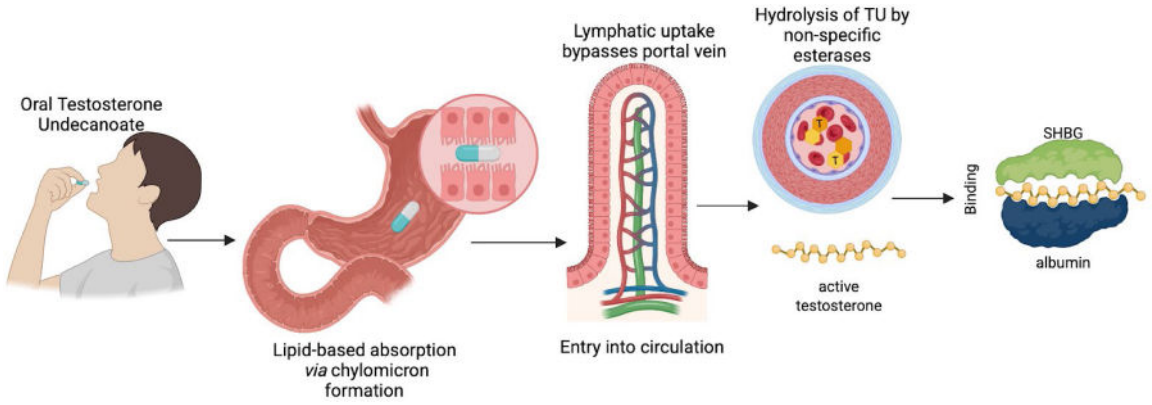

Fig. 4. Absorption pathway of oral testosterone undecanoate. Oral testosterone undecanoate (TU) is absorbed in the intestine via lipid-mediated emulsification and chylomicron formation, facilitating lymphatic transport that bypasses first-pass hepatic metabolism. TU enters systemic circulation through intestinal lymphatic vessels and undergoes hydrolysis by non-specific esterases in the blood vessels to release active testosterone. Circulating testosterone then binds to sex hormone-binding globulin (SHBG) and albumin, regulating free hormone availability and systemic androgenic effect [55–56]. Image created in BioRender (www.biorender.com).

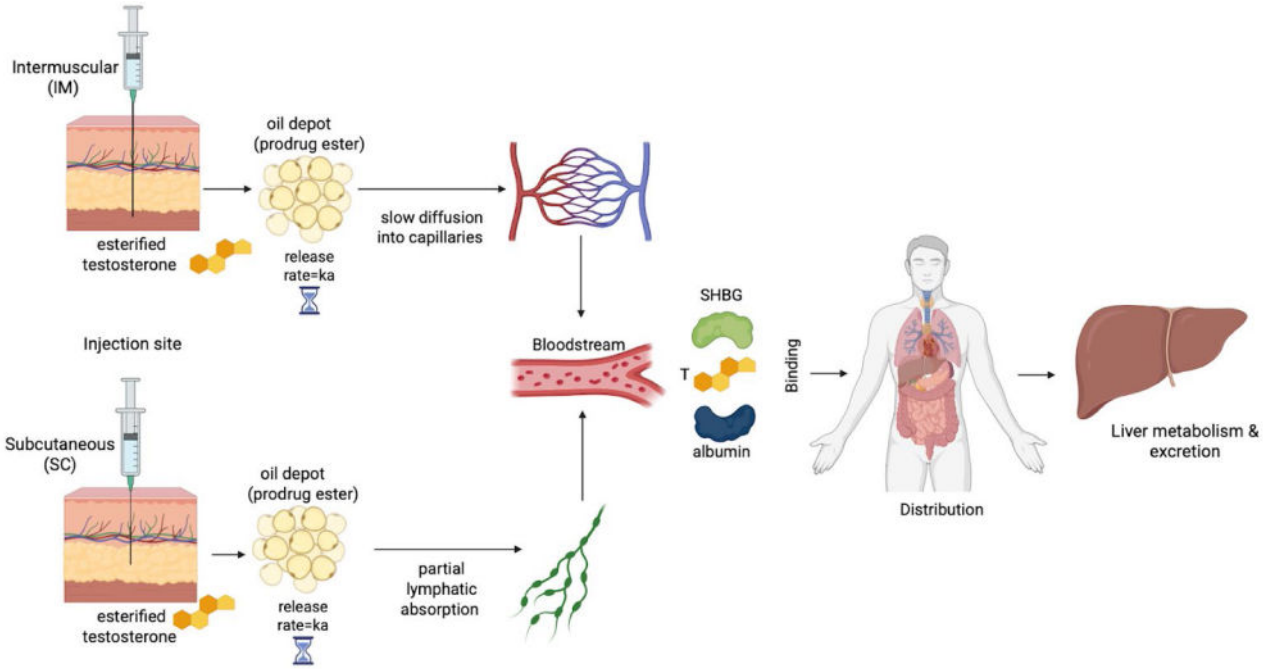

Fig. 5. Pharmacokinetic disposition of intramuscular (IM) and subcutaneous (SC) injectable testosterone esters. Esterified testosterone is delivered into either muscle or subcutaneous tissue, forming a depot within the oily excipient. The rate-limiting step for systemic exposure is the slow release of esterified drug from the depot into nearby capillaries (absorption rate constant, k_a). IM administration facilitates direct vascular uptake, whereas SC injection additionally undergoes partial lymphatic absorption. Once in circulation, esterases cleave the ester to release active testosterone, which binds to sex hormone-binding globulin (SHBG) and albumin for systemic transport. Testosterone distributes into androgen-responsive tissues before undergoing hepatic metabolism and subsequent excretion. Depot-driven absorption kinetics underpin the prolonged and formulation-dependent exposure profiles of long-acting injectable testosterone therapies [64–65]. Image created in BioRender (www.biorender.com).

glycol (PEG 300), with PG achieving a peak solvent flux of ~10.8 μg/cm^2/h across human epidermis, indicative of superior permeability and skin affinity [53]. While that study used ibuprofen as a model active, the mechanistic principles can extend to lipophilic steroids like testosterone.

8.1.2. Oral TU

Native oral testosterone undergoes extensive first-pass hepatic metabolism, rendering it clinically ineffective [54]. Testosterone undecanoate (TU), a lipophilic ester prodrug, was developed to bypass this limitation through intestinal lymphatic absorption rather than entry into portal circulation and extensive first pass hepatic metabolism [55]. After uptake, TU is hydrolyzed by non-specific esterases into active testosterone, largely bypassing first-pass metabolism [56]. Older oil-based TU formulations, such as Andriol® Testocaps were highly dependent on dietary fat to stimulate chylomicron formation, which facilitated lymphatic transport. Co-administration with high-fat meals (>19 g) could increase serum testosterone concentrations by more than tenfold compared to fasting conditions, resulting in inconsistent lymphatic uptake that is dependent on variations in dietary fat content [54,55,57].

Newer self-emulsifying drug delivery systems (SEDDS), such as Jatenzo® and Kyzatrex®, encapsulate TU in lipid–surfactant mixtures

that spontaneously form microemulsions in the gastrointestinal tract [55]. This enhances solubilization and promotes more consistent lymphatic transport, thereby reducing dependence on dietary fat [55,58,59]. At steady state, Jatenzo® achieved a mean serum testosterone concentration (C_{avg}) of approximately 34.9 ± 20.1 nmol/l, indicating stable systemic exposure under fed conditions. Notably, food and fat content had no significant influence on peak testosterone levels (C_{max}), highlighting the formulation's reduced dependence on dietary fat for absorption [55]. In a phase III trial of Kyzatrex®, 88 % of subjects achieved a peak testosterone concentration of ≤ 41.64 nmol/l, indicating consistent control of serum levels [60].

The PK characteristics of oral TU and topical administration differ substantially. Data from Swerdloff *et al.* (2020) and Miner et al. (2025) show that while both oral and topical testosterone achieve eugonadal mean 24 h serum concentrations (C_{avg24}: 13.97 and 13.29 nmol/l, respectively), oral TU consistently generates higher peak concentrations [55,61]. In Swerdloff's study, oral TU produced a C_{max} of 34.79nmol/l compared to 23.05nmol/l for transdermal therapy [55]. This reflects the rapid intestinal lymphatic uptake and subsequent hydrolysis of oral TU into release of free testosterone into systemic circulation. This process results in a bolus-like entry of testosterone into systemic circulation, characterized by sharp peaks and relatively consistent T_{max} values (2–6 hrs). In contrast, transdermal testosterone exhibits a highly variable T_{max} (0–24hr), where individuals reached peak concentrations at widely varying times [55,62]. This variability reflects inter- and intra- differences in skin permeability, hydration status, and reservoir kinetics.

In a phase III study by Miner *et al.* (2025), PK profiling of oral TU in hypogonadal males demonstrated how oral TU can mimic the circadian rhythm of endogenous testosterone secretion [61]. At Week 3, the serum C_{avg24} was 17.16 ± 6.69 nmol/l, and the C_{max} reached 45.36 ± 22.64 nmol/l [61]. By Week 13, C_{avg} decreased slightly to 15.48 ± 5.95 nmol/l, with a corresponding C_{max} of 39.37 ± 18.25 nmol/l, remaining within the physiological eugonadal range. T_{max} was noted as early as 2 hours post-dose, with serum concentrations peaking by 6 hours and declining back to baseline within 12 hours. These findings suggest a pulsatile absorption profile that may mimic the circadian rhythm of endogenous testosterone secretion [19]. This is further highlighted in the simulated model Fig. 4. Notably, Pastuszak *et al.* (2021) suggests that formulations mimicking physiological pulsatility may offer advantages, particularly in younger men [40]. These findings reiterate that Oral TU, with defined dosing intervals, produces distinct peaks that resemble endogenous rhythms, while transdermal preparations offer lower, steadier concentrations with reduced peak-trough fluctuations [63]. Therefore, oral TU may better approximate natural testosterone fluctuations, though the clinical relevance of this remains to be fully established.

8.1.3. Injectable testosterone

Injectable testosterone esters, testosterone enanthate (TE), cypionate (TC), and undecanoate (TU); differ fundamentally from oral and transdermal formulations in that absorption is governed by depot kinetics rather than mucosal or cutaneous diffusion [64]. Following IM or SC injection, the esterified testosterone is slowly released from the oily depot into the interstitial fluid and systemic circulation (Fig. 5) [64]. The slow liberation of esterified testosterone from the depot occurs at a rate slower than systemic clearance [65]. Therefore, we can assume flip-flop kinetics ($K_a < K_{el}$) [66].

The rate and extent of absorption are determined by both the physicochemical properties of the ester (e.g., chain length, lipophilicity) and the characteristics of the depot site (muscle vs subcutaneous fat), producing formulation-specific half-lives (Table 1).

Injectable TE, containing a 7-carbon ester chain in a sesame oil vehicle, demonstrates similar depot-mediated absorption with a slightly shorter duration of action compared to TC, typically requiring administration every 1–2 weeks [19]. IM TE 100 mg reaches a C_{max} of ~30nmol/l and T_{max} of 24–48 hours, producing higher peak-to-trough variability within each dosing interval compared to long-acting TU [67].

Injectable TC, formulated in cottonseed oil with an 8-carbon ester chain, exhibits moderately sustained absorption kinetics from the intramuscular depot, permitting dosing every 1–2 weeks [19]. IM TC at 200 mg every 2 weeks produces a mean C_{max} of ~38.6 nmol/l and T_{max} of 4–5 days, exhibiting moderate-to-high fluctuations in serum testosterone compared with long-acting TU [40].

Injectable TU, with an 11- carbon side chain in castor oil, displays even slower absorption kinetics compared to TE or TU owing to its longer ester chain and depot formulation, permitting dosing every 10–14 weeks [19]. IM TU 1000 mg reaches an average C_{max} of ~42nmol/l and T_{max} of ~7–14 days, producing a lower peak-to-trough variability within each cycle compared to TE or TC [40,68].

Population modelling and simulation studies of injectable TU confirm flip-flop kinetics where absorption is the rate limiting step, resulting in terminal half-life of several weeks and minimal accumulation at steady state [63]. Notably, absorption of injectable TU may be influenced by inter-patient variability as lower body weight is associated with faster k_a, while heavier men exhibit slower absorption and larger apparent volume of distribution (V/F) [63].

8.1.4. Depot site and injection volume effects on absorption

Depot location influences absorption through differences in vascular perfusion, tissue composition, and depot stability [69]. Compared to SC injections, IM typically results in faster absorption due to higher vascular density of skeletal muscle and more rapid drug diffusion from the oil depot to neighboring capillaries [70,71]. This enhances the concentration gradient driving diffusion out of the depot. By contrast, subcutaneous tissue contains more adipose cells, lower perfusion, and a looser extracellular matrix, which collectively slows diffusion [64]. Although T_{max} is delayed in SC, both routes ultimately yield comparable systemic exposure at steady state. In a crossover study of TU, 1000 mg in 4 ml castor oil, T_{max} was delayed in SC administration (~8.0 days) versus IM (~3.3 days) though C_{max} and AUC were not significantly different [72] (Fig. 6).

Injection volume affects the depot's geometry by further modulating the dissolution and diffusion rate [73]. A larger volume usually forms a more consolidated mass with a lower surface area-to-volume ratio, slowing the surface-mediated dissolution of ester into the surrounding interstitial fluid [44,74,75]. In the context of testosterone formulations, these principles may help explain why the long-acting TU in large-volume castor oil depots exhibits very prolonged absorption ($t_{1/2}$ ~53 days) [63]. These findings suggest that combination of high viscosity and large depot mass delays release dramatically.

8.2. Distribution

Testosterone is a moderately lipophilic steroid (logP ≈ 3.3) with extensive protein binding and tissue-specific metabolism, which promotes broad distribution across highly perfused tissues and enables penetration into lipid-rich compartments such as adipose and muscle [76]. PK models of testosterone formulations generally employ a linear one-compartment distribution model with first order absorption and elimination [63,77].

The volume of distribution (V_d) of testosterone is determined primarily by the physicochemical properties of the drug (protein binding, tissue affinity, lipophilicity) and interindividual variability (weight, plasma proteins, disease states) [75]. Whilst different testosterone formulations don't directly affect testosterone's intrinsic V_d, they can change the rate and extent of absorption into systemic circulation, causing changes in the apparent V_d when modelling PK [77].

The distribution of testosterone in the body is significantly influenced by its binding to plasma proteins, primarily SHBG, human serum albumin (HSA) and to a lesser extent, corticosteroid binding globulin (CBG) and Alpha-1-acid glycoprotein (AGP) [78,79]. As demonstrated in Fig. 7, approximately 43–45 % of testosterone is bound to SHBG with

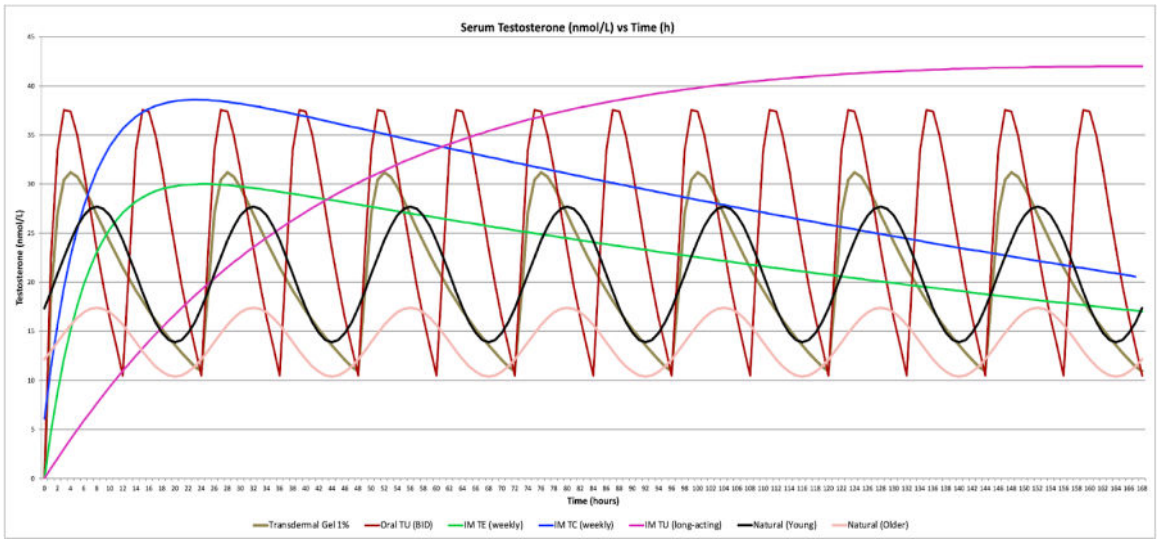

Fig. 6. Simulated serum testosterone concentration–time profiles over 1 week following different routes of testosterone. Pharmacokinetic profiles were simulated using the Bateman function to model first-order absorption and elimination kinetics, where K represents the elimination rate constant, K_a the absorption rate constant, and S a scale factor used to normalise the simulated C_{max} (plasma concentration) for each of the formulations. These parameters were manually calculated based on half-life, time-to-peak, and dosing intervals data sets from published clinical studies [40,72,85]. Steady-state conditions were replicated across each dosing interval (24 hours for transdermal gel 1 %, 12 hours for oral undecanoate, and 168 hours for injection esters). The (black) curve represents the natural circadian rhythm of healthy young men (aged 18–35), while the (pink) curve represents typical profiles for older men (>35). Circadian testosterone patterns were modelled using a cosine function, while mean and amplitude values were chosen to produce physiological morning peaks and evening troughs observed in population data [40]. Curves for each of the testosterone replacement therapies show typical mean concentration-time profiles for transdermal testosterone gel 1 % (khaki), oral testosterone undecanoate (Oral TU)(deep red), intramuscular testosterone enanthate (IM TE)(green), intramuscular testosterone cypionate (IM TC)(dark blue), and intramuscular testosterone undecanoate (IM TU)(plum). All curves were constructed in Excel using parameterised equations to visualise expected plasma fluctuation patterns across a one-week dosing cycle.

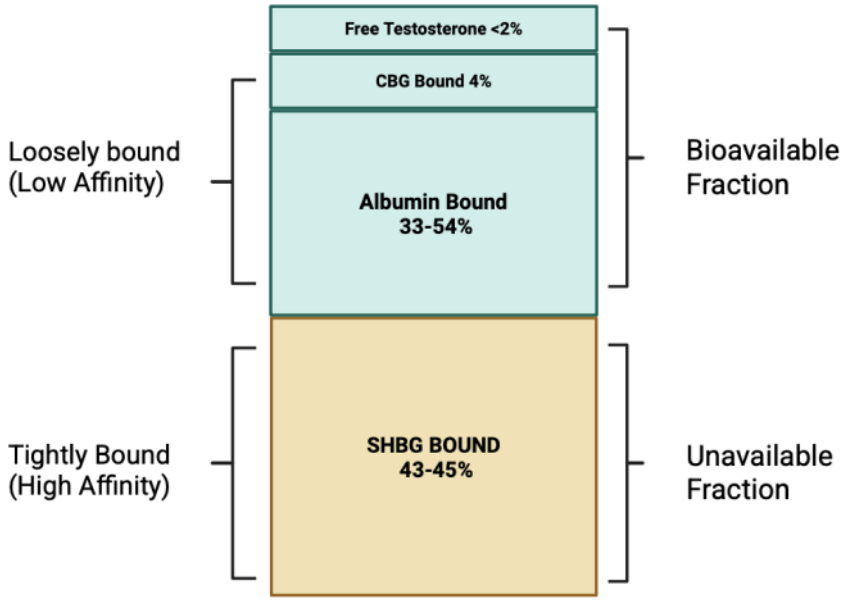

Fig. 7. Plasma distribution of testosterone among binding compartments. The majority of circulating testosterone is protein bound, with ~43–45 % tightly bound to sex hormone–binding globulin (SHBG) and 33–54 % loosely bound to albumin. The combined free fraction (< 2 %), albumin- and corticosteroid binding globulin-bound (CBG) fractions constitute the bioavailable pool that can diffuse into target tissues (~43–64 %) [78–80]. Image created with Biorender (www.Biorender.com).

high affinity which is biologically inactive and unavailable for tissue uptake. Binding of testosterone to one subunit of SHBG dimer, induces a conformational change that alters the binding characteristic of the second site [78]. This leads to allosteric modulation of the second testosterone-binding event. This model suggests that SHBG serves more than just a passive carrier but actively regulates free testosterone levels [78,80,81]. Fluctuations in SHBG levels modulate the free fraction available for metabolism [63]. This indirectly influences apparent clearance (CL/F), where a decrease in SHBG levels has been associated with an increase in CL/F [63]. HSA accounts for 60 % of total serum protein and due to its high binding capacity, 33–54 % of testosterone binds with low affinity (k_a 2.0–4.1 × 10^4 l/mol), forming a readily dissociable and bioavailable pool. CBG binds up to 4 % of circulating testosterone with low binding affinity (K_a 5.4 × 10^6 l/mol). Therefore,

the term bioavailable testosterone refers to the sum of circulating testosterone that is unbound to SHBG (1–4 %), plus HSA-, CBG- and AGP-bound testosterone (~39–60 %) [78]. This fraction represents the portion capable of exerting therapeutic effects and undergoing metabolism and excretion [78].

While all testosterone replacement therapies exhibit high plasma protein binding, differences in formulation can alter the free, unbound fraction and consequently, tissue distribution. In the next subparagraphs, we will discuss how different routes of administration impact the distribution of testosterone.

8.2.1. Oral

Oral TU has been associated with higher free testosterone concentrations compared to topical formulations [55,61,82]. The liver, the primary site of SHBG synthesis, is exposed to higher androgen concentrations following oral TU compared to transdermal routes [55]. Even though oral TU is designed for lymphatic absorption (to bypass hepatic first-pass effect), a fraction of the absorbed dose still reaches the hepatic circulation, enough to activate hepatic AR's [55]. The fraction of TU that undergoes intestinal (~89 %) and hepatic (~9 %) first-pass metabolism is small compared to the magnitude of hepatic exposure during systemic clearance [19,83]. This direct hepatic androgenic stimulation downregulates hepatic SHBG synthesis [55,61,82]. A study by Swerdloff et al. 2020 showed oral TU reduced serum SHBG concentrations by 30–40 %, compared to a 9 % reduction following topical formulations [55]. In a 2024 retrospective, 6-month, high-dose TU cohort, conducted by Vo *et al.* 2024, SHBG dropped from ~32.4 nmol/l to 17.83 nmol/l (45 % decrease) [82]. With significant reductions in SHBG synthesis, a lower portion of testosterone is tightly bound and subsequent increases in calculated free testosterone are observed [78]. This is despite an overall reduction in concentration of the active drug, due to higher first-pass effect compared to injections and transdermal formulations in which completely avoid first pass hepatic metabolism [55].

8.2.2. Transdermal

Currently, studies exploring the distribution parameters of transdermal testosterone formulations, particularly in comparison to other dosage forms are lacking. Precise V_d estimates for transdermal testosterone are not readily reported. Following transdermal absorption through the stratum corneum, testosterone enters the dermal microvasculature directly, bypassing hepatic first-pass metabolism. As observed in a 2000 randomized control trial conducted by Swerdloff *et al.*, this results in a small, clinically insignificant reduction (~9 %) in serum SHBG levels in comparison to oral TU (55). Thus, the percentage of free testosterone did not change significantly following transdermal T treatment, as it did following oral TU [55].

A study conducted by Meikle *et al.* reports the half-life of transdermal testosterone to be ~1.3 hours, where hypogonadal concentrations are achieved within 24 hours of patch removal [84]. This short half-life suggests that transdermal delivered testosterone is primarily confined to the central compartment, with limited deep tissue uptake compared to long-acting IM esters. High plasma protein binding further restricts its free fraction, which results in a smaller apparent V_d [84].

8.2.3. IM injection

Injectable testosterone esters like TC, TE and TU bypass first-pass hepatic metabolism but remain subject to systemic hepatic clearance. Unlike oral formulations, IM injections exert minimal sustained effects on SHBG, though transient reductions in SHBG may occur following supraphysiologic peaks right after injection (which normalize over time) (Wang *et al.* 2013). Ultimately, IM formulations maintain a consistent protein-binding profile.

Population PK models for depot IM testosterone esters often use a one-compartment model to represent the distribution of total testosterone after injection [63,77]. These models estimate the apparent V_d of IM TC to be between 12.4–14.4kL, IM TU 12.2kL and IM TE 13.8kL as a population-mean model parameter for total testosterone [63,77]. Notably, when TE was injected as SC the V_d increases significantly to 23.8 kl likely reflecting slower absorption kinetics and more prolonged systemic exposure, which leads the PK model to interpret the drug as distributing into a larger volume than when administered IM [85]. Such a large V_d and half-life reflects testosterone's high lipophilicity and high affinity to tissue proteins, allowing extensive distribution into well-perfused tissues (liver, kidney, prostate, skeletal muscle), and slower equilibration in adipose depots [86].

A 2019 study by Turner et al. compares the PK parameters produced by IM and SC testosterone injections and demonstrates that the SC route produces near identical systemic exposure to IM injection [72]. The use of a bi-exponential model in Turner et al. supports a two-compartment PK process, where comparable findings have been reported with SC administration of TU, in relation to IM injection [72].

Interindividual variability in weight and serum albumin, and their changes from baseline, have also been identified as significant covariates for total testosterone [53,81]. It is estimated that a heavier male (110 kg) has 1.58 times higher V_d compared to that of a male of the median weight (85 kg) [81]. This increase in V_d can be attributed to a greater tissue mass in heavier individuals, which serve as a distribution reservoirs for a lipophilic drug like testosterone [86].

8.2.4. Summary

Oral formulations that undergo hepatic metabolism result in the significant downregulation of SHBG synthesis, causing a notable increase in free testosterone. Transdermal, IM & SC injectable testosterone each follow a two-compartment model of distribution, with a clinically insignificant effect on SHBG, and therefore no change in unbound testosterone. Large apparent V_d values are observed in IM and SC injections, which increase with the patient's body weight. Overall, apparent and true V_d values of testosterone replacement therapies are not readily reported in pharmacokinetic studies, particularly with respect to specific formulations and how their distribution throughout the body compares to each other.

8.3. Metabolism

The metabolism of testosterone is governed predominantly by the liver whereby Phase I (oxidative/reductive) and Phase II (conjugative) pathways occur [67,87]. However, the extent and site of metabolism can vary significantly depending on the route of administration. Differences in enzymatic exposure, bypass of first-pass metabolism, and tissue-specific enzyme activity all contribute to formulation-dependent pharmacokinetics [87]. In this section we discuss how major testosterone dosage forms transdermal, oral, and injectable esters differ in terms of metabolic site, enzyme involvement, and biotransformation pathways. Table 2 summarizes these comparisons.

8.3.1. Phase I metabolism

As illustrated in Fig. 8, testosterone undergoes extensive Phase I metabolism, in which functional groups are introduced or exposed through oxidation or reduction [87]. The most clinically significant reductive pathway is conversion by 5α-reductase to DHT, a metabolite with two to threefold higher affinity for the AR [88].

In the context of transdermal administration, the conversion of testosterone to DHT is particularly relevant because the skin itself expresses significant 5α-reductase activity [89]. Human skin keratinocytes and fibroblasts carry both type 1 and type 2 isoforms of 5α-reductase and locally can convert permeating testosterone into DHT before it even reaches systemic circulation [90–92]. This is most pronounced with applications to the scrotum, which generate disproportionately high serum DHT/testosterone ratios compared with oral or injectable routes [43]. In a study by Iyer *et al.* (2017), serum DHT concentrations were quantified using liquid chromatography–mass spectrometry following administration of varying doses of testosterone cream [43]. Results

Table 2
Metabolism of testosterone across therapeutic formulations.

Formulation	Metabolic Enzymes	Phase I Metabolism	Phase II Metabolism	Notes	References
Transdermal	Skin: 5α-reductase Liver: CYP3A4, UGT2B17	Skin: Conversion to DHT Liver: 6β-, 16β-hydroxy testosterone	Glucuronidation (UGT2B17) Sulfation (SULT2A1)	Cutaneous 5α-reduction may elevate DHT systemically. Application site affects local metabolism.	43,93
Oral prodrug	Esterases → CYP3A4, UGT2B17	TU → T *via* hydrolysis T → 6β-hydroxy, 16β-hydroxy testosterone	Same as above	Lymphatic absorption bypasses first-pass hepatic metabolism initially. Still undergoes hepatic metabolism post-absorption.	48, 55, 93
IM/SC TE/TC prodrug	Esterases → CYP3A4, UGT2B17	TE/TC → T *via* ester hydrolysis T → DHT, E2, 6β/16β-hydroxy testosterone	Same as above	Rapid enzymatic hydrolysis by nonspecific plasma esterases yields testosterone available for hepatic metabolism. Transient surges enhance CYP19A1 and 5α-reductase activity.	93,63,85
IM/SC TU prodrug	Esterases → CYP3A4, UGT2B17	TU → T *via* hydrolysis T → DHT, E2, 6β/16β-hydroxy testosterone	Same as above	Extremely slow ester hydrolysis limits hepatic exposure per unit time, reducing enzyme saturation and minimizing aromatase induction. Metabolic clearance primarily governed by gradual liberation from depot.	40,93

Abbreviations: Intramuscular (IM), Subcutaneous (SC), Testosterone (T), Dihydrotestosterone (DHT), Testosterone ethanoate (TE), Testosterone cypionate (TC), estradiol (E2).

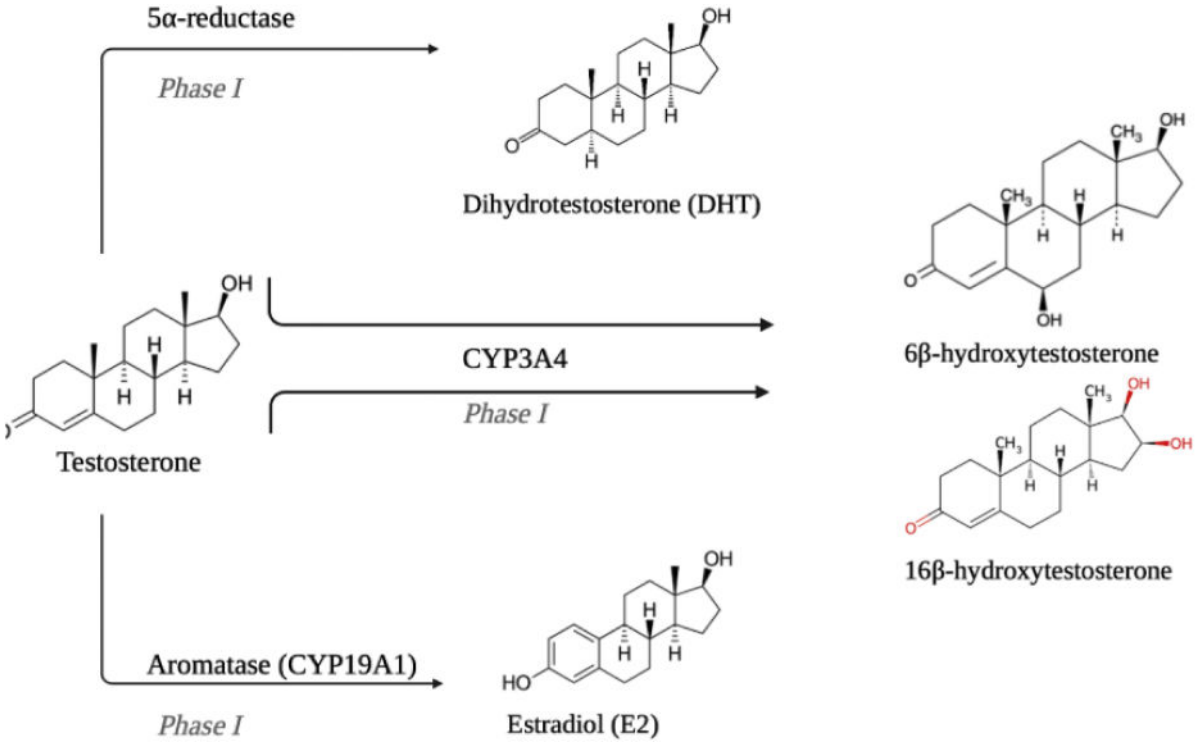

Fig. 8. Primary Phase I metabolic pathways of testosterone. Testosterone undergoes oxidative and reductive biotransformation catalyzed by key enzymes in Phase I metabolism. The 5α-reductase pathway converts testosterone to dihydrotestosterone (DHT), a more potent androgen that mediates many peripheral androgenic effects. The aromatase enzyme (CYP19A1) catalyzes the aromatization of testosterone to estradiol (E2), facilitating androgen–estrogen balance. The cytochrome P450 enzyme CYP3A4 mediates hydroxylation reactions to yield 6β-hydroxytestosterone and 16β-hydroxytestosterone, major oxidative metabolites involved in hepatic clearance and urinary excretion. Structures were generated to illustrate the principal enzymatic routes governing testosterone metabolism [93]. Image created with Biorender (www.Biorender.com).

demonstrated a significant increase in DHT levels ($P < 0.0001$), rising to 1.0–1.4 ng/ml in a time-dependent, but not dose-dependent manner, with peak concentrations observed at approximately 4.9 hours post-application. In contrast, oral TU does not disproportionately increase DHT [55]. Oral TU is absorbed through the lymphatic system and carried by the thoracic duct into systemic circulation, where it is converted into testosterone, avoiding the portal vein and reducing first pass metabolism in the liver. Hydrolysis occurs primarily in the systemic circulation, yielding a more physiologic DHT / testosterone balance compared to transdermal [48,55].

In addition, testosterone undergoes limited oxidative metabolism catalyzed primarily by hepatic cytochrome P450 enzymes, most significantly by CYP3A4 to generate hydroxylated metabolites 6β-hydroxytestosterone, 16β-hydroxytestosterone and several less abundant derivatives [93]. In parallel, aromatase (CYP19A1) catalyzes the conversion of testosterone to estradiol (E2), a metabolite essential for bone integrity, cognitive function, feedback regulation and neuroendocrine signaling [94]. While physiologic aromatization is beneficial, excessive

estradiol may contribute to gynecomastia and fluid retention, particularly with high-peak injectable regimens [94]. As illustrated in Fig. 6, Short-acting testosterone esters such as TC and TE produce sharp surges in serum testosterone shortly after injection, often exceeding physiological upper limits within 24–48 hours. These supraphysiologic peaks not only drive increased aromatase activity, especially in adipose-rich or estrogen-sensitive tissues but also result in pronounced fluctuations in estradiol levels over the dosing interval [28,63]. Moreover, this peak–-trough variability has been associated with a higher incidence of estrogen-mediated side effects, especially when shorter-acting esters or higher doses are used without appropriate monitoring or dose titration [28,40,63]. In contrast, long-acting TU, displays a flatter PK profile with lower peak-to-trough ratios. This more stable serum testosterone concentration limits the abrupt surges that potentiate aromatization, thereby reducing the risk of estradiol-related adverse effects [28,40,63,93].

8.3.2. Phase II metabolism

Phase II metabolism renders testosterone and its active metabolites water-soluble for excretion. As seen in Fig. 9, about 50 % of circulating testosterone undergoes direct conjugation at the 17B-hydroxyl group, mediated by UGT2B17 to form testosterone-glucuronide (TG) [95]. To a lesser extent, sulfation is mediated by SULT2A1, producing testosterone-sulphate (TS). These conjugation reactions increase polarity, facilitating renal excretion. Interindividual variability, especially UGT2B17 deletion polymorphisms, significantly influences urinary excretion and contributes to both pharmacokinetic heterogeneity and challenges in anti-doping detection [81].

In summary, while all testosterone formulations ultimately undergo similar hepatic Phase I and Phase II metabolism, the route of administration significantly influences the extent and site of metabolic transformation. Transdermal gels exhibit increased local conversion to DHT due to high 5α-reductase activity in the skin, contributing to a higher DHT:testosterone ratio relative to other delivery systems. In contrast, oral TU formulations undergo lymphatic absorption only partially undergoing first-pass hepatic metabolism, leading to the formation of conjugated metabolites prior to systemic entry. Injectable esters, which bypass first-pass metabolism entirely, demonstrate the most efficient systemic bioavailability. However, shorter-acting esters such as TE can transiently elevate 5α-reductase and aromatase activity due to rapid serum concentration peaks, whereas long-acting TU injections provide a steadier hormonal profile with less pronounced metabolic fluctuation. Collectively, these distinctions underscore that while metabolic pathways remain conserved, formulation-dependent pharmacokinetics shape the relative balance of active and inactive androgenic metabolites in clinical practice.

8.4. Excretion

Renal clearance represents a minor elimination pathway for testosterone, as the majority of the hormone is excreted in the form of conjugated metabolites [28]. Since < 2 % of circulating testosterone exists in the unbound form, glomerular filtration contributes negligibly to total clearance [28,78]. Therefore, we can assume that the fraction of testosterone excreted unchanged (Fe) is extremely low. Additionally, any unbound testosterone that does enter the nephron is highly lipophilic and undergoes extensive passive reabsorption within the distal tubule, resulting in minimal to no change in testosterone levels found in urine [96].

Instead, testosterones clearance predominantly occurs through urinary excretion of its hydrophilic conjugated metabolites (TG and TS) [28]. These water-soluble glucuronide and sulphate conjugates are actively secreted into the tubular lumen by organic anion transporters (OATs) within the proximal nephron, a process responsible for nearly 90 % of testosterone-derived metabolites detected in urine [87,97–99]. In contrast, 6–10 % of metabolites are excreted *via* the biliary route into faeces, primarily as unconjugated molecules [100]. TG and TS elimination is largely secretion-driven due to their hydrophilic nature,

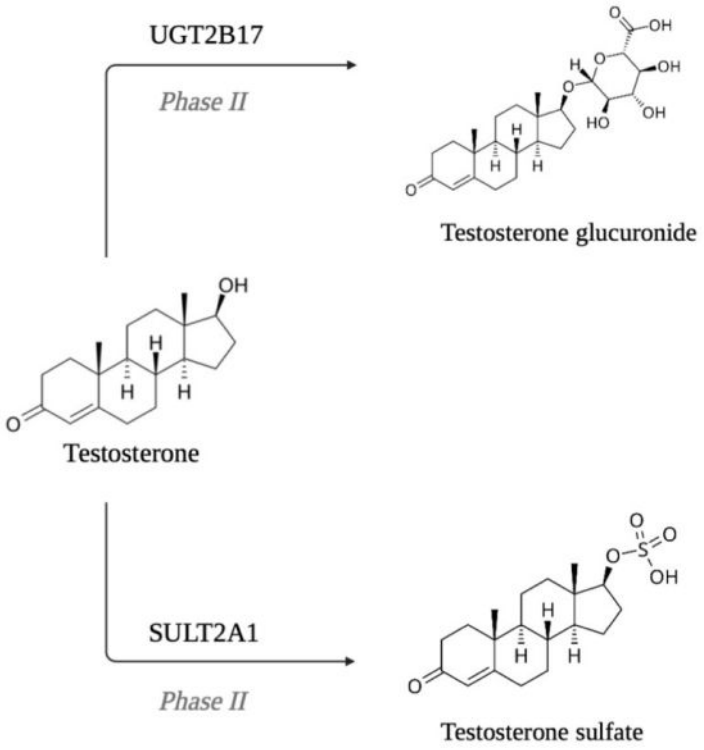

Fig. 9. Phase II metabolism of testosterone via conjugation pathways. Testosterone undergoes glucuronidation catalyzed by UGT2B17 to form testosterone glucuronide and sulfation mediated by SULT2A1 to yield testosterone sulphate. These conjugative reactions enhance water solubility and facilitate renal elimination of androgen metabolites [93]. Image created with Biorender (www.Biorender.com).

reflecting their reliance on active transporter systems for the movement of conjugated metabolites [101]. Within hepatocytes, these conjugates are exported through ATP-binding cassette (ABC) efflux transporters before entering either bile or systemic circulation for renal elimination [87,101]. An experimental study on human efflux transport systems have identified multidrug resistance–associated proteins 2 and 3 (MRP2/ABCC2 and MRP3/ABCC3) as key mediators responsible for exporting androgen glucuronide metabolites from hepatocytes into bile and blood, respectively [98]. While the route of administration primarily influences absorption and extent of systemic exposure of TRT, the findings of Li et al. (2019) suggest that downstream excretion kinetics are indirectly dependent on MRP2/MRP3-mediated transport [87]. Collectively, these findings demonstrate that testosterone clearance relies on Phase II conjugation followed by active tubular secretion, providing mechanistic evidence explaining why more than 90 % of administered testosterone is ultimately recovered in urine as glucuronide and sulphate conjugates [99,102].

Excretion of testosterone is metabolism-dependent rather than route-of-administration-dependent, as the effectiveness of metabolite production will influence the volume of metabolites for excretion. The choice of formulation can influence entry into circulation, the rate and extent of exposure, and the magnitude of first-pass effect, which may result in alteration of metabolite profiles and excretion patterns [103].

Oral TU undergoes partial first-pass metabolism in the intestine and liver, resulting in substantial glucuronide formation in enterocytes and hepatocytes [55,87]. Here, MRP3-mediated basolateral efflux may allow glucuronides to re-enter systemic circulation [104]. In the gastrointestinal lumen microbial beta-glucuronidases can deconjugate glucuronide metabolites of TU, releasing free testosterone which may be reabsorbed *via* enterohepatic recycling [87]. Reabsorption may modulate the exposure of active androgen, increasing its apparent systemic half-life and in turn decreasing the rate of elimination [87].

The apparent clearance (CL/F) of testosterone is reduced by increases in circulating SHBG levels or decreases in hepatic blood flow or liver function [28,63]. As discussed in the Section 8.2, oral TU downregulates hepatic SHBG synthesis, increasing free circulating testosterone. This may increase the amount of free substrate available for hepatic enzymes to metabolize, potentially increasing glucuronide formation and MRP2-mediated biliary export [28]. Greater biliary output could expand the pool of conjugates available for microbial deconjugation and enterohepatic recycling.

Injectable testosterone esters exhibit markedly different clearance characteristics determined by their ester chain length, oil vehicle, and depot release kinetics rather than intrinsic hepatic metabolism [19]. Because injections bypass intestinal and first-pass metabolism, the fraction of conjugated metabolites recovered in urine is lower per dose compared with oral TU, but total systemic exposure is higher due to systemic absorption and near-complete bioavailability [56]. CL/F varies inversely with ester length and depot stability as expressed in Table 1. Thus, short-acting esters display rapid systemic peaks and higher apparent clearance.

IM TE has an ester chain length of 7-carbons, producing CL/F value of 50l/h and a terminal half-life of ~7 days [85]. Notably, differences in injection sites alter clearance values. SC injection seems to yield slightly higher clearance (60.8 l/h) compared to IM [85]. TC has an ester chain length of 8-carbons, producing a CL/F value of 110 l/h and a terminal half-life of ~8 days [77]. These preparations typically require administration every 1–2 weeks to maintain eugonadal concentrations. In contrast, the long chain TU ester (11 carbons), suspended in viscous castor oil exhibits much slower diffusion and enzymatic cleavage, resulting in CL/F value of 198 l/h and a terminal half-life of ~53 days [63].

Collectively, injectable preparations demonstrate the highest apparent clearance, reflecting absorption-limited flip-flop kinetics rather than intrinsic metabolic clearance [66]. These findings explain why injection administration exhibits the most prolonged elimination phase, and delayed urinary metabolite recovery among testosterone delivery systems, reflecting their depot-controlled release and high systemic bioavailability [28].

PK compartment modeling by Han T et al. 2008 demonstrate that transdermal testosterone gels and creams exhibit moderate apparent clearance values (CL/F ~49.4 l/h) and produce steadier serum testosterone concentrations for 1 % gel formulations compared to oral formulations [105]. This is primarily due to their sustained percutaneous absorption and avoidance of first-pass hepatic metabolism [61]. Upon application, the formulation's hydroalcoholic vehicle facilitates partitioning into the stratum corneum, from which testosterone diffuses gradually into the dermis and systemic circulation over 12–24 hours [106]. This slow and continuous absorption prolongs CL/F by maintaining plasma concentration above the metabolic clearance rate of free testosterone [55,107]. Consequently, the effective terminal half-life extends to ~15 hours, markedly longer than the intrinsic plasma half-life of 10–100 min of unesterified testosterone once in systemic [41,106]. Furthermore, the absence of pre-systemic metabolism markedly reduces the proportion of dose converted to conjugates immediately after administration, producing lower urinary recovery of testosterone-glucuronide compared with oral TU [108].

9. Pharmacodynamic mechanisms of testosterone in type 2 diabetes

Pharmacodynamics (PD) describes the relationship between testosterone exposure and its downstream biological effects, encompassing the cascade of molecular, cellular, and metabolic responses that arise from AR activation [27,109]. In the context of TRT and T2D, these effects include modulation of glucose metabolism, insulin sensitivity, and body composition which are secondary to PK profiles [32]. As discussed in Section 8, testosterone formulations differ significantly in their absorption profiles, serum concentration variability, and impact on SHBG, all of which shape the intensity and duration of AR-mediated signaling. This section explores how testosterone's PK behavior across formulations governs its PD effects on glucose regulation and metabolic homeostasis in men with T2D.

The metabolic effects of TRT are intrinsically linked to the PK characteristics of its dosage form and ester kinetics, which determine the pattern and stability of AR engagement. The course of TRT's metabolic benefits in hypogonadal men with T2D reflects the time required for sustained AR activation to remodel metabolic tissue and restore insulin responsiveness [27]. Saad *et al.* 2011 demonstrates that early endocrine responses, such as improved insulin sensitivity and reduced inflammatory cytokine expression, may rise within a few weeks of initial TRT [17]. In contrast, measurable improvements in HbA_1c, lipid profiles and body composition changes typically require prolonged exposure to therapies of at least 6 to 12 months [17,110]. This gradual trajectory suggests that TRT's metabolic efficacy is progressive and reliant on maintaining stable physiologically appropriate testosterone concentrations.

9.1. *Long-acting formulations*

The T4DM randomized controlled trial examined men at high risk of diabetes who received long-acting IM TU injections (1000 mg) every 3 months alongside a standard lifestyle program. Over two years, the TU-treated group showed about a 40 % *relative* reduction in progression from prediabetes toT2D compared to placebo (12 % vs 21 % incidence; RR ~0.59). Testosterone therapy also led to greater improvements in glycemic indices. Notably, the TU group had a larger decrease in 2-hour oral glucose tolerance test (OGTT) glucose levels (mean ~0.75 mmol/l lower than placebo; $P < 0.0001$). These results indicate that long-acting TU injections can significantly improve glucose tolerance and reduce diabetes incidence when added to lifestyle intervention. Importantly, the T4DM trial reported this benefit independent of baseline

testosterone levels, suggesting the effect was attributable to therapy rather than selection bias [27]. Furthermore, in a long-term, real-world registry study, Haider and Saad (2020) evaluated the metabolic impact of long-acting IM TU every 12 weeks in 178 hypogonadal men with established type 2 diabetes, followed for up to 11 years. Men receiving TU demonstrated progressive and sustained improvements in glycemic and metabolic parameters throughout follow-up. Mean HbA₁c declined steadily from 9.0 ± 1.1 % to 5.9 ± 0.4 %, while fasting glucose and insulin levels decreased in parallel, reflecting markedly enhanced insulin sensitivity (HOMA-IR fell from 10.2 to 1.7 in those achieving remission). These metabolic gains coincided with substantial reductions in body weight (−22.7 kg) and waist circumference (−12.8 cm), alongside pronounced declines in total and LDL cholesterol and triglycerides. Notably, 34.3 % of men achieved complete remission of T2D, defined as maintaining HbA₁*c* < 6.5 % without glucose-lowering medication, and an additional 46.6 % achieved normoglycemia while continuing therapy. No remissions occurred among untreated controls, whose metabolic markers worsened over time [110].

These findings suggest that sustained physiological testosterone exposure achieved with long-acting IM TU can elicit durable improvements in insulin sensitivity, adiposity, and overall glycemic control, with a subset of men achieving remission of T2D. Mechanistically, this may reflect the PK profile of long-acting formulations, which maintain relatively stable serum testosterone concentrations and thereby enable continuous AR activation (Table 1). Sustained AR engagement promotes steady transcriptional modulation of genes regulating glucose transport, lipid oxidation, and mitochondrial biogenesis, while supporting metabolic homeostasis through AMPK–GLUT4 pathway activation, suppression of hepatic gluconeogenesis, and reductions in visceral adiposity and pro-inflammatory cytokines [111].

9.2. Short acting formulations

In contrast, Dhindsa et al. (2016) evaluated short-acting IM TE 250 mg administered every two weeks for 24 weeks in 44 men with T2D and hypogonadotropic hypogonadism. Treatment produced significantly improved insulin sensitivity, evidenced by an increase in glucose infusion rate during the hyperinsulinemia euglycemic clamp, which increased by ~32 % in the testosterone group compared to no change in placebo. These metabolic benefits were accompanied by a mean increase in lean body mass of +3.4 kg and a decrease in subcutaneous fat mass of −3.3 kg, though visceral and hepatic fat volumes did not significantly change. The expression of key adipose tissue insulin-signaling genes (IR-β, IRS-1, Akt-2, GLUT4) was also upregulated, and circulating levels of inflammatory markers (free fatty acids, CRP, IL-1β, TNF-α, leptin) fell significantly. Despite this, HbA1c levels remain unchanged over the 24 weeks [112].

These findings can be mechanistically explained because short-acting injectable esters, such as TE, produce rapid systemic peaks followed by steep troughs, resulting in intermittent receptor stimulation (Fig. 6). This oscillatory exposure enhances anabolic effects on muscle mass but often fails to produce consistent improvements in insulin sensitivity or glycemic control due to fluctuating concentrations and transient metabolic signaling. These fluctuations could theoretically create setbacks in the overall metabolic benefit of TRT [112]. Fluctuating testosterone levels can disrupt normal glucose metabolism [16]. Transient supraphysiologic peaks may increase aromatization to estradiol, which alters insulin sensitivity, while low troughs reduce androgen-mediated stimulation of glucose uptake and muscle anabolism in skeletal tissue [8,113]. Therefore, maintaining consistent testosterone exposure is crucial for preserving insulin sensitivity. Furthermore, the study was only conducted for 24 weeks. Saad et al. (2011) reported that TRT's metabolic time course is staggered with early improvements in insulin sensitivity (days-weeks), however intermediate changes in inflammation and Hba1c are observed at 3–12 months [17]. This may indicate that if the study conducted by Dhindsa et al. (2016) was extended to 12 months there may have been changes in HbA1c levels [112].

SC testosterone delivery maintains a stable androgenic environment that supports favorable metabolic functions [27,114]. As discussed in Section 8.1, SC injection may produce a flatter concentration curve evidenced by a significantly longer T_{max} compared to IM (Table 1, Fig. 6). This reduces significant peaks and troughs which may more consistently activate AR receptors contributing to more pronounced insulin signaling and glucose regulation in muscle and adipose tissue [14]. The stable hormonal exposure achieved by SC dosing appears to sustain continuous AR activation and downstream metabolic signaling, supporting steadier insulin sensitivity. Unlike IM dosing, which produces sharp testosterone peaks that decline gradually and induce cyclical metabolic variability, SC delivery maintains a more physiologic exposure profile, minimizing fluctuations that can disrupt metabolic homeostasis [67,115]. This aligns with findings from TRT trials such as T4DM and TIMES2, which have linked stable TRT to improving glucose levels and body composition.

9.3. Transdermal

The TIMES2 trial provides a clear illustration of how transdermal testosterone's PK shapes its metabolic outcomes. In this 12-month randomized, placebo-controlled study of 220 hypogonadal men with T2D and/or metabolic syndrome, daily application of a 2 % testosterone gel produced gradual and sustained improvements in insulin resistance. A decrease in HOMA-IR by ~15 % at 6 months and ~16 % at 12 months was observed. Moreover, modest benefits in lipid parameters and waist circumference, with a small transient reduction in HbA₁c at month 9 was also observed. This can be mechanistically explained as transdermal gels deliver continuous percutaneous input that yields a flat 24-h serum profile with low fluctuation when applied daily and titrated. That kinetic stability is consistent with gradual, cumulative PD effects on insulin sensitivity and adiposity rather than large HbA1c drops over 6–12 months. TIMES2 operationalized this with protocolized dose titration and testosterone checks ~2 h post-application, aiming to keep TT in a physiologic window. Although the study was conducted for 12 months, it seems that transdermal testosterone gels can improve metabolic parameters in men with T2D or metabolic syndrome, but their effects are modest, variable, and depend heavily on achieving stable physiological exposure and good adherence [32].

Gels have lower peak/trough swings than injections, good for safety/hematocrit but that also means no large acute glycemic shifts, instead incremental IR improvements over time [32,61]. The stable hormonal pattern achieved by daily gel application mimics endogenous circadian testosterone rhythms, which minimizes excessive fluctuations producing lower peak/troughs than injections [116]. This controlled delivery of transdermal gels results in steady plasma levels throughout the dosing interval [40]. Furthermore, as endogenous testosterone naturally follows a circadian rhythm, these physiological oscillations are slight and regulated, supporting stable AR activation and normal metabolic homeostasis [8]. In contrast, sharp pharmacokinetic peaks and low troughs produced by short-acting esters are non-physiological and may destabilize glucose regulation as well as insulin signaling in patients [63]. Therefore, maintaining consistent testosterone exposure may be crucial in preserving insulin sensitivity [64,117].

9.4. Oral

Oral testosterone formulations such as TU, are absorbed *via* the lymphatic system, producing short-lived peaks and relatively low troughs [55]. Consequently, oral TU must be administered daily, often twice daily, to maintain physiologic concentrations, yet serum fluctuations remain greater than with transdermal or long-acting injectable delivery systems (Fig. 6). Metabolically, oral TRT has been less studied in men with T2D, this may be due to the challenge of consistently

achieving and sustaining therapeutic testosterone levels [61]. It is plausible that the transient pharmacokinetic peaks after each oral dose may suffice for androgenic effects on libido/energy, whereas the limited cumulative exposure may reduce the anabolic and insulin-sensitizing benefits seen with more sustained testosterone exposure. However, direct comparative data are lacking.

10. Limitations

Despite the ongoing research on TRT, there are still several limitations across the vast number of studies specializing in this area of research. Extensive heterogeneity exists across the trials and studies, including the differences in study design, patient populations, and the duration of treatment. Variability in population characteristics such as age, hormone levels, environmental exposure, and medical conditions further expands the heterogeneity across the studies. Notably, the lack of direct comparative PK studies across testosterone formulations made it difficult to conduct an accurate analysis and tabulation of data. Calculating valid averages of PK values across the available studies was limited by variations in multiple factors like dosage administered, duration of study, whether mean or median values were calculated, and whether serum or plasma T concentrations were measured. In Section 8.2, we hypothesize that the downregulation of hepatic SHBG synthesis following oral TU, may increase the enterohepatic recycling of testosterone metabolites, and thus decrease the rate of elimination. Transporter expression, saturation kinetics, and intestinal microbiome activity add additional layers of variability that complicate prediction of the net effect. To test this relationship empirically, further comparative PK studies could quantify SHBG levels, plasma and urinary glucuronide metabolites, and efflux following oral and non-oral administration.

To address these limitations, future research should prioritize well-controlled, comparative PK and PD studies across testosterone formulations under standardized conditions. Direct head-to-head trials comparing oral, transdermal, and injectable preparations in matched cohorts would clarify how route-dependent kinetics translate to metabolic outcomes in men with T2D. In parallel, incorporating population PD modelling and stratification by SHBG genotype, body composition, and insulin resistance could help explain interindividual variability in drug exposure and response.

Additionally, further research may expand on the preclinical research done by Al-Trad et al. (2019) which investigated gold nanoparticles (AuNPs) as regulators of testosterone-related tissue effects [118]. In a model of rats with testosterone-induced benign prostatic hyperplasia, AuNPs reflected size-dependent inhibition of the progression of prostatic hyperplasia. Smaller 20 nm particles reduced prostatic inflammation and pro-inflammatory markers, whereas larger particles were found to worsen these processes. The findings of this study suggest the influence of nanoparticle size 8 on the biological response to testosterone and also highlight the vitality of particle size in the effect of therapeutic outcomes. Although this research is preclinical, there is immense potential present for the introduction of nanoparticle-based delivery systems in improving oral/transdermal testosterone formulations.

It would be beneficial to expand on the emerging studies conducted by Moradi Hasan-Abad *et al.*, (2022), which explore biosensor testosterone monitoring [119]. These digital systems demonstrate the potential for testosterone serum tracking in real time and the incorporation of them in TRT, which could allow for real-time feedback monitoring and automatic dosing to maintain steady serum levels. This would assist in managing serum fluctuations and optimize testosterone exposure.

11. Conclusion

The PK and PD relationship of testosterone formulations demonstrate that the route of administration dictates hormonal stability and metabolic outcomes in hypogonadal men with T2D. Transdermal formulations deliver testosterone gradually though the stratum corneum, achieving steady systemic absorption that mimics endogenous diurnal rhythms. However, absorption is highly site-dependent, with scrotal application producing markedly greater bioavailability and enhanced conversion to DHT due to local 5α-reductase activity. Oral TU utilizes intestinal lymphatic transport to partially bypass first pass hepatic metabolism, achieving rapid yet transient systemic peaks. Modern self-emulsifying formulations (e.g., Jatenzo®, Kyzatrex®) have reduced food dependence and improved absorption consistency, but much like transdermal preparations, still display pulsate exposure and short elimination half-lives. Hepatic exposure of oral formulations is linked to downregulation of hepatic SHBG synthesis, resulting in a larger portion of free testosterone within systemic circulation capable of exerting therapeutic effects. However, the total serum testosterone concentration is lower compared to other formulations. Transdermal and oral formulations may offer rhythmic AR activation however, the shorter exposure window limits sustained metabolic impact compared to longer-acting routes. Clinically, this can enhance anabolic effects, however, this oscillatory exposure may not consistently or adequately improve insulin sensitivity or glycemic control. Short-acting injectable esters exhibit rapid depot release and pronounced peak-trough variability, with supraphysiological peaks occurring within 24–48 hours post injection. These surges transiently stimulate aromatase and 5α-reductase activity, elevate estradiol and DHT formation. Transdermal, oral and short acting esters produce an oscillatory kinetic profile, intermittently stimulating ARs, and supporting anabolic effects. However, this can produce unstable enhanced glucose metabolism and insulin responsiveness. Long-acting testosterone esters exhibit absorption-limited (flip-flop) kinetics, yielding a flatter, prolonged serum profile over 10–14 weeks. This stable kinetic profile maintains continuous AR engagement, steady AMPK-GLUT4 signaling, and consistent suppression of gluconeogenic activity, enhancing insulin sensitivity and glycemic regulation compared to other formulations.

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CRediT authorship contribution statement

Omar Aboelela: Writing – review & editing, Writing – original draft, Validation, Software. **Sarah Al Asaad:** Writing – review & editing, Writing – original draft, Visualization, Validation. **Alannah-Mona Ajami:** Writing – review & editing, Writing – original draft, Validation. **Jeyda Olca:** Writing – review & editing, Writing – original draft. **Sarah Davies:** Writing – review & editing, Writing – original draft, Validation, Software. **Josleen Abo Saad:** Writing – review & editing, Writing – original draft. **Suzan Rizqou:** Writing – review & editing, Writing – original draft. **Gabriele De Rubis:** Writing – review & editing, Visualization, Validation, Resources, Project administration, Conceptualization. **Kamal Dua:** Writing – review & editing, Visualization, Validation. **Keshav Raj Paudel:** Writing – review & editing, Visualization, Validation, Supervision, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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