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Intracrinology and Testosterone Pellet Therapy: An Enzyme-Aware, Symptom-Driven Approach to Hormone Optimization in Aging

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Abstract

Intracrinology refers to the local synthesis, activation, and inactivation of sex steroids within peripheral tissues from precursor hormones such as dehydroepiandrosterone (DHEA), androstenedione, and testosterone (T). This process occurs largely independent of circulating hormone levels. With aging, declining adrenal and gonadal androgens create tissue-specific hormone imbalances that contribute to common symptoms in both men and women, including loss of muscle and bone mass, reduced libido, mood disturbances, low energy, and increased body fat.

Conventional testosterone replacement therapy (TRT) guidelines focus on restoring serum testosterone to mid- or upper-normal ranges for young men, or to premenopausal levels in women, to avoid pharmacologic dosing. However, these serum-centric approaches fail to account for the critical role of intracrine production. In peripheral tissues, most bioactive testosterone, dihydrotestosterone (DHT) via 5α-reductase, and estradiol (E2) via aromatase are produced locally from adrenal precursors rather than from circulating testosterone alone.

Continuous-release subcutaneous testosterone pellet therapy delivers stable physiologic levels of testosterone for 3-6 months. This provides a consistent substrate that allows tissues to produce DHT and E2 on demand, according to local enzyme activity, without the peaks and troughs associated with gels, injections, or oral formulations. The result is an enzyme-aware, symptom-driven model that prioritizes clinical symptom relief, individual enzyme profiles, and side effect patterns over strict serum targets.

This narrative review explores the roles of steroidogenic enzymes across organ systems, the tissue-specific effects of testosterone, DHT, and estradiol, strategies for managing conversion imbalances (including adjunctive aromatase and 5α-reductase inhibitors), the limitations of serum estradiol monitoring, and observational evidence supporting higher steady-state testosterone levels for effective intracrine restoration in aging populations. While promising for individualized hormone optimization with acceptable safety in monitored patients, this approach requires validation through large-scale randomized controlled trials.

Categories: Family/General Practice, Obstetrics/Gynecology, Endocrinology/Diabetes/Metabolism
Keywords: 5α-reductase, aging hormones, aromatase, dhea decline, hormone replacement therapy, intracrinology, local steroid metabolism, steroidogenic enzymes, testosterone pellets, testosterone replacement therapy (trt)

Introduction And Background

Progressive age-related declines in testosterone (T) and adrenal precursor androgens (dehydroepiandrosterone (DHEA) and androstenedione) affect both men and women [1-5]. In men, total and free T decrease by approximately 1% per year after age 40, contributing to late-onset hypogonadism [6]. In women, declines often start in the mid-30s and intensify through perimenopause and postmenopause, independent of ovarian function, leading to impairments in sexual function, energy, mood, musculoskeletal integrity, and overall quality of life [1,5]. These changes elevate risks for clinical hypogonadism (prevalence of 7%-20% in men over 40 [6]) and associated comorbidities in both sexes [7].

Guidelines from the Endocrine Society, American Urological Association (AUA), and European Association of Urology recommend restoring serum T to mid-normal ranges for young men, with monitoring of trough or mid-cycle levels, hematocrit, and prostate-specific antigen (PSA) [3,8-11]. However, this serum-centric framework falls short in the context of intracrinology, the tissue-specific, on-demand biosynthesis and inactivation of active sex steroids (dihydrotestosterone (DHT) via 5α-reductase; estradiol (E2) via aromatase) from circulating precursors [1]. Adrenal precursors account for 20%-50% of androgenic activity in adult men and over 80% in postmenopausal women, yet their profound age-related reduction creates substrate deficiency in peripheral tissues, even when serum T appears “normal” [4,5].

Continuous-release subcutaneous T pellet therapy mitigates this by providing stable physiologic T levels over 3-6 months, serving as a consistent substrate for intracrine enzymes and enabling restoration of tissue-

specific DHT and E2 without the fluctuations inherent in injections, gels, or oral preparations [3]. Far from being merely another delivery option, this modality supports a new therapeutic paradigm: enzyme-aware and symptom-driven dosing that targets resolution of clinical symptoms, objective markers (e.g., bone density and validated quality of life scores), and individualized side effect profiles rather than rigid serum targets [6,12-14]. Effective intracrine balance in aging patients, especially women, frequently necessitates steady-state serum T levels above conventional norms to offset lost adrenal contribution [4,5].

Literature search and selection

This narrative review synthesizes the current understanding of intracrinology and its implications for testosterone replacement therapy in aging populations. Relevant literature was identified through searches of PubMed/MEDLINE and Google Scholar, supplemented by manual screening of reference lists from seminal articles and targeted specialty journals. The search emphasized English-language peer-reviewed publications from 2000 to 2025, with greater weight given to more recent studies (2015-2025).

Articles were included if they addressed intracrine steroid metabolism, tissue-specific sex steroid conversion, limitations of serum-based testosterone monitoring, subcutaneous testosterone pellet therapy, enzyme modulators (such as aromatase or 5α-reductase inhibitors), or clinical symptom management in aging or hypogonadal men and women. Both original research and expert reviews were considered. Publications were excluded if they focused solely on non-human models without translational relevance, addressed unrelated endocrine conditions, or were non-peer-reviewed.

Consistent with standard narrative review methodology, no formal risk of bias assessment or Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) framework was applied. Instead, priority was given to high-quality, clinically relevant sources, with limitations of the evidence base (particularly the predominance of observational data) acknowledged throughout the review.

Review

Steroidogenic enzymes, primarily cytochromes P450 (CYPs) and hydroxysteroid dehydrogenases (HSDs), catalyze the biosynthesis and interconversion of steroids from cholesterol or precursors [15,16]. In peripheral tissues, they facilitate intracrine actions, with expression varying by organ to meet local needs [17]. This section focuses on two key enzymes central to testosterone metabolism: 5α-reductase (SRD5A1/2/3), which irreversibly reduces T to DHT, amplifying androgen signaling, and is primarily expressed in the prostate, skin, hair follicles, liver, and brain [18], and aromatase (CYP19A1), which aromatizes T and androstenedione to E2 and estrone, respectively, and is primarily expressed in adipose tissue, bone (osteoblasts), brain, breast, vascular endothelium, and gastrointestinal tract [16].

These enzymes enable tissue-specific regulation: for instance, increased aromatase in aging adipose tissue elevates E2 conversion, while declining 5α-reductase in skin reduces DHT-dependent effects [19].

Organ- and tissue-specific effects of testosterone, estradiol, and dihydrotestosterone

The biologically active hormones T, E2 (derived from T via aromatase), and DHT (from T via 5α-reductase) exert tissue-specific effects through nuclear receptors (AR for T/DHT; ERα/β for E2) and non-genomic pathways [14]. Effects vary by sex due to differences in hormone levels and receptor expression, with aging exacerbating imbalances. Table *1* summarizes the organ-specific effects of T, E2, and DHT (adapted and synthesized from Glaser and Dimitrakakis [13], Labrie [14], Labrie et al. [17], and Simpson et al. [19], with enzyme-specific tissue distributions informed by Russell and Wilson [15], Simpson et al. [16], and Azzouni et al. [18]).

Organ system	T effects	E2 effects	DHT effects
Reproductive	Promotes spermatogenesis, libido, erectile function, prostate growth (men); follicular growth, libido (women)	Supports spermatogenesis, sperm motility, libido (men); regulates ovulation, uterine function (women)	Drives prostate development/growth, male secondary characteristics; minor role in spermatogenesis
Breast	Anti-proliferative; may protect against cancer	Promotes proliferation; increases breast cancer risk	Anti-proliferative similar to T
Skeletal	Enhances bone formation, density, maturation; prevents sarcopenia/osteopenia	Suppresses resorption, maintains BMD; anti-osteoporotic	Contributes to bone integrity via AR; enhances BMD with T
Muscular	Increases mass, strength, protein synthesis; reverses sarcopenia	Supports insulin sensitivity, lipid oxidation; protects bioenergetics	Enhances sensitivity, protein synthesis in sarcopenic fibers
Cardiovascular	Improves function, reduces lipids/metabolic syndrome; enhances cardiomyocyte metabolism	Vasoprotective, reduces atherosclerosis; improves endothelial NO	Increases insulin sensitivity; potential metabolic risks in excess
Nervous	Maintains cognition, mood; neuroprotection	Regulates memory, libido; neuroprotective versus ischemia	Modulates signaling in glial cells; indirect behavioral influence
Endocrine	Regulates HPG axis, insulin sensitivity; interacts with GH	Feedback on GnRH/LH/FSH; insulinotropic in pancreas	Supports AR-mediated endocrine functions
Integumentary	Influences hair/gland function; synthesized in skin	Regulates metabolism	Regulates sebaceous glands, hair growth; causes male-pattern baldness
Urinary	Supports bladder, prostate/kidney function	Maintains mechanisms via reproductive interplay	Critical for prostate development
Adipose	Limits deposition, reduces visceral fat; improves body composition	Suppresses adipogenesis, reduces inflammation/fibrosis	Reduces adiposity, increases insulin sensitivity
Liver	Regulates glucose/protein metabolism; improves steatosis	Inhibits lipid synthesis; improves function	Regulates glucocorticoid action/metabolic phenotype
Immune	Modulates inflammation via local production	Modulates responses; protects neurons/angiogenesis	Indirect via androgen regulation
Hematopoietic	Stimulates erythropoiesis; thrombosis risk	Limited; telomere length association	Not extensively detailed
Respiratory	Improves lung function (FEV1, FVC); suppresses inflammation; benefits in COPD	Influences lung function; may promote inflammation/oxidative stress	Improves lung function (FEV1, FVC)
Gastrointestinal	Interacts with gut microbiota; supports local steroid metabolism	Regulates microbiota diversity; hormone metabolism	Similar to T; intestinal deglucuronidation/metabolism

TABLE 1: Organ- and tissue-specific effects of T, E2, and DHT

T: testosterone, E2: estradiol, DHT: dihydrotestosterone, BMD: bone mineral density, AR: androgen receptor, HPG: hypothalamic-pituitary-gonadal, GH: growth hormone, GnRH: gonadotropin-releasing hormone, LH: luteinizing hormone, FSH: follicle-stimulating hormone, NO: nitric oxide, FEV1: forced expiratory volume in one second, FVC: forced vital capacity, COPD: chronic obstructive pulmonary disease

Adapted and synthesized from Glaser and Dimitrakakis [13], Labrie [14], Labrie et al. [17], and Simpson et al. [19], with enzyme-specific tissue distributions informed by Russell and Wilson [15], Simpson et al. [16], and Azzouni et al. [18]

Testosterone as substrate for local conversion to estradiol and DHT

Continuous-release testosterone from subcutaneous pellet implants serves a dual role: it directly stimulates androgen receptors throughout the body and, equally important, provides a steady substrate for local intracrine enzymes in peripheral tissues. This enables on-demand, tissue-specific production of E2 and DHT without the supraphysiologic peaks or subphysiologic troughs that disrupt homeostasis with other delivery methods [3].

In tissues expressing aromatase (e.g., adipose tissue, bone, brain, breast, and vascular endothelium), testosterone is converted to E2. Local intracellular E2 concentrations can reach levels up to 15-fold higher than in plasma, particularly in postmenopausal women [14]. In tissues expressing 5α-reductase (e.g., prostate, skin, hair follicles, liver, brain, and urogenital tract), testosterone is irreversibly reduced to DHT, the most potent androgen, thereby amplifying androgen receptor signaling where needed [18].

Clinical consequences of unbalanced conversion and their management

Excessive Aromatase Activity Leading to Elevated Estradiol

In men, it leads to gynecomastia, erectile dysfunction, infertility, depression, loss of libido, fatigue, mood instability, increased body fat, loss of muscle mass, and hair loss. In women, it results in breast tenderness, bloating, weight gain, headaches, mood instability, decreased libido, irregular or heavy menstrual bleeding, and worsening premenstrual symptoms. Management involves aromatase inhibitors, most commonly anastrozole, often co-implanted in the pellet [13,20,21].

Excessive 5α-Reductase Activity Leading to Elevated DHT

In men, it can lead to possible prostate issues, male-pattern baldness, and acne. In women, it causes hirsutism, acne, and scalp hair loss. Management involves 5α-reductase inhibitors (finasteride or dutasteride), also frequently co-implanted [15,18].

Overall, steady testosterone delivery using pellets facilitates local tissue-specific hormone conversion. Adjunctive use of enzyme inhibitors, when required, should be highly individualized, focusing on balancing physiologic benefits with potential adverse effects, and not applied automatically for all patients, other than aromatase inhibitors in patients with hormone receptor-positive breast cancer [13].

Serum testosterone levels on therapy versus endogenous reference ranges

Current guidelines recommend restoring serum total testosterone to mid-normal ranges for young men while avoiding supraphysiologic levels, with monitoring of trough or mid-cycle values, hematocrit, and PSA [8-10]. For women, the 2019 Global Consensus Position Statement advises that blood testosterone concentrations on therapy should approximate premenopausal physiologic values [22]. These serum-centric frameworks, however, do not account for the principles of intracrinology and the fundamentally different physiologic context that exogenous testosterone therapy creates.

In healthy young adults, endogenous reference ranges reflect a state in which robust adrenal precursor pools (DHEA, DHEA-S, and androstenedione) simultaneously supply substrate for intracrine conversion in every peripheral tissue, independent of circulating testosterone [1,4,5,14,17]. Serum testosterone in this setting represents only a fraction of total androgenic activity; the majority of bioactive androgens (and, in women, virtually all estrogens) are synthesized, act, and are inactivated within target cells through intracrine mechanisms [1,14,17].

With aging, DHEA declines by an average of 60% by menopause in women and 70%-95% cumulatively by old age, and androstenedione falls by approximately 50% between ages 40 and 70 [4,5,23]. In men, total and free testosterone decline by roughly 1% per year after age 40, compounded by parallel reductions in adrenal precursors [2,6]. This progressive substrate depletion creates a tissue-level androgen and estrogen deficit far more severe than serum testosterone alone suggests, particularly in women, where serum testosterone may decline only 15%-22% across the menopausal transition despite a dramatic reduction in total intracrine androgen production as reflected by glucuronidated androgen metabolites (androsterone glucuronide (ADT-G) and androstane-3α,17β-diol-G (3α-diol-G)) [4,23,24]. Notably, Labrie et al. demonstrated in 377 postmenopausal and 47 premenopausal women that serum testosterone shows no correlation with these metabolites, confirming that it cannot serve as a reliable measure of total androgenic activity in women [24].

When continuous-release testosterone pellets are administered to an aging patient, the exogenous testosterone must serve as a primary circulating substrate for local intracrine conversion to DHT and E2, not only replacing the diminished gonadal contribution but also compensating for the profound deficit in adrenal precursors that would normally supply the intracrine machinery independently [4,5,14]. Consequently, achieving physiologic tissue-level effects frequently requires steady-state serum testosterone concentrations that exceed traditional reference ranges, a concept described as “pharmacologic dosing for physiologic effect” [6,12,13,25].

Clinical data confirm this principle. In women treated with subcutaneous testosterone implants (approximately 2 mg/kg), mean serum testosterone at four weeks was 299 ± 107 ng/dL, 4-6 times the upper limit of endogenous normal, yet was associated with symptom resolution without clinically significant

androgen excess [25]. Substantial inter-individual variability due to differences in body composition, tissue vascularization, enzyme expression profiles, sex hormone-binding globulin (SHBG) concentrations, and androgen receptor sensitivity renders any single testosterone measurement inherently unreliable as a sole guide to therapeutic adequacy in either sex [21,25].

Estradiol monitoring during testosterone pellet therapy: limits of serum measurements

Estradiol activity during continuous-release testosterone pellet therapy is largely determined by intracrine aromatization within peripheral tissues, and these locally generated levels are often not accurately reflected by routine serum assays [1,12-14,17,19,21]. Aromatase expressed in adipose tissue, bone, brain, breast, vascular endothelium, and gastrointestinal tract converts testosterone to estradiol within target cells, where intracellular estradiol may reach concentrations many-fold higher than plasma, particularly in postmenopausal women [1,14,17]. Because estradiol produced in this manner is rapidly bound and inactivated locally, appreciable changes in serum estradiol occur only when local production exceeds tissue binding and metabolic capacity and "spills over" into the circulation [1,17,19].

In this intracrine framework, monitoring of estradiol during pellet therapy should prioritize clinical symptoms and tissue-specific side effects, such as breast tenderness (gynecomastia), abnormal uterine bleeding, bloating and fluid retention, mood lability, vasomotor instability, or lack of effect from testosterone therapy, rather than strict adherence to a universal numeric "target range" for serum estradiol in otherwise healthy hypogonadal men and peri- and postmenopausal women [12,13,16,19,21]. Many pellet-treated patients remain asymptomatic with serum estradiol concentrations below 30 pg/mL, and there is no evidence-based requirement to escalate estradiol to higher "replacement" thresholds if key endpoints (libido, bone preservation, vasomotor control, mood, and urogenital comfort) are achieved [12,13,17,21].

An important exception is advanced hormone-sensitive breast cancer, where the therapeutic objective is pharmacologic suppression of estradiol to the lowest feasible level. Outside this oncologic context, however, no universally accepted target serum estradiol range has been defined for patients on testosterone pellets. Maintaining estradiol levels below approximately 30 pg/mL, with close monitoring of clinical symptoms, is consistent with the intracrine model of tissue-specific estrogen regulation and is supported by available long-term observational data [1,12-14,17,21].

Conclusions

Continuous-release testosterone pellets provide a steady substrate for intracrine production of estradiol and dihydrotestosterone, compensating for substantial age-related losses in both testosterone and adrenal androgen precursors. Observational data in both men and women demonstrate that pharmacologic pellet dosing, often producing serum testosterone above traditional young-adult norms, particularly in women, can be used safely with vigilant monitoring. In women, sustained improvements in quality-of-life scores, musculoskeletal and vasomotor symptoms, sexual function, and mood are consistently reported, including in breast cancer survivors, with cancer incidence and recurrence rates comparable to or below population norms. Preclinical and clinical evidence further suggests that androgens may counteract estrogen-driven proliferation in breast tissue, although these observations require confirmation in large randomized controlled trials.

Testosterone pellet therapy restores organ-level hormonal control by supplying sufficient testosterone for direct androgen receptor activation and as substrate for local intracrine enzymes, often without mandatory systemic estradiol supplementation. Outcomes demonstrate clear dose dependency, with best results achieved by titrating to symptom resolution and adverse effect surveillance (e.g., erythrocytosis, symptoms of excess estrogen, and skin and body hair changes) rather than mid-range serum targets. When selectively employed, adjunctive low-dose aromatase or 5α-reductase inhibitors (often combined in the pellet implant) correct conversion imbalances while preserving stable substrate delivery. Judicious integration of enzyme modulators and lifestyle interventions yields durable symptom relief in both sexes with acceptable safety under appropriate monitoring. Large, long-term randomized trials are needed to definitively establish this enzyme-aware approach in clinical practice.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

Concept and design: Rebecca Glaser

Acquisition, analysis, or interpretation of data: Rebecca Glaser

Drafting of the manuscript: Rebecca Glaser

Critical review of the manuscript for important intellectual content: Rebecca Glaser

Disclosures

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