Chapter 2
Pathophysiology of Late-Onset Hypogonadism and Risks and Benefits of Replacement Therapy

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Introduction

The testosterone molecule is depicted below (Fig. 2.1).

Testosterone is primarily produced by Leydig cells of the testicles in response to LH (luteinizing hormone) stimulation from the pituitary gland, and within the target cell, it is broken down into DHT (dihydrotestosterone) and E2 (estradiol). DHT is the active component which gives the androgenic effects. The adrenal glands mainly produce its precursor dehydroepiandrosterone (DHEA) and contribute a small amount of testosterone to the sum total. In utero during development the effects of testosterone on the target organs are depicted in Fig 2.2.

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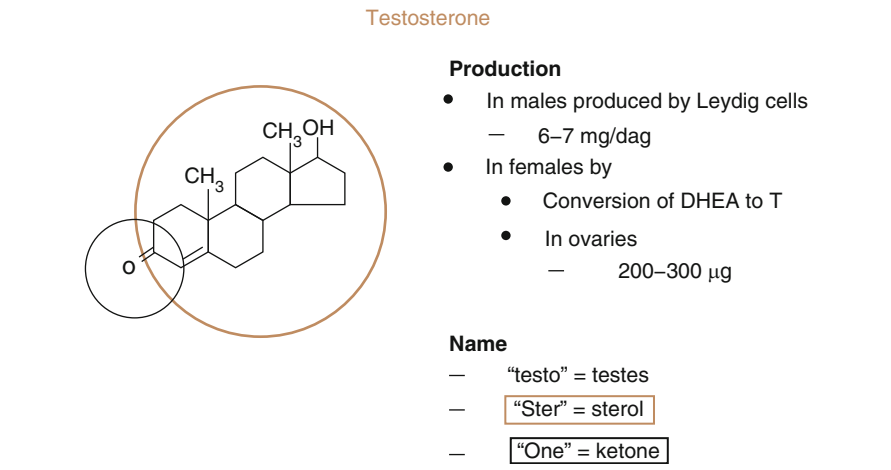

Fig. 2.1 Molecular structure of testosterone

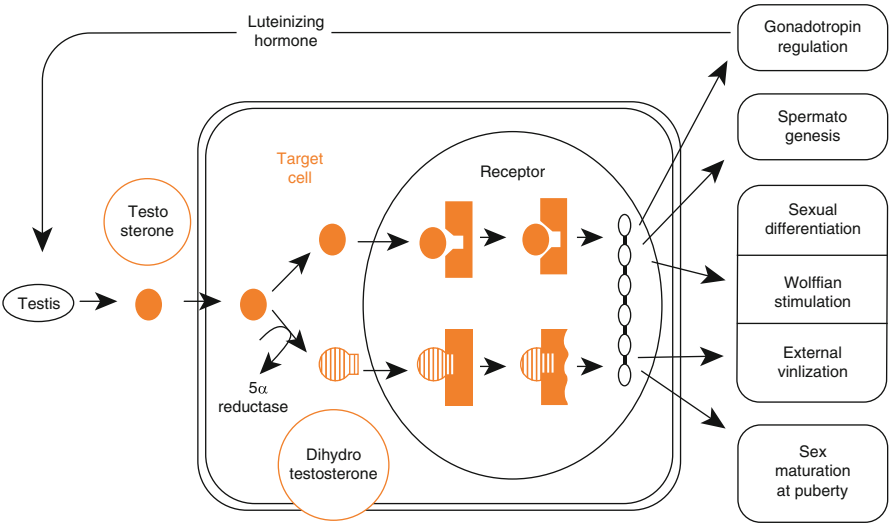

Fig. 2.2 Testosterone and its effects on various target organs (Griffin 1992)

Testosterone: Physiological Effects

- CNS – libido, energy, spatial cognition, well-being, memory
- Larynx – lowers voice
- Liver – lowers SHBG and HDL
- Kidney – raises erythropoietin

- Prostate – increases size and secretions
- Genitals – development, erections, spermatogenesis
- Skin – increases facial and body hair and sebum production
- Blood – increases hematocrit
- Adipose tissue – increases lipolysis, decreases abdominal fat
- Bone – increases bone mineral density
- Muscle mass – increases lean mass and strength

Sexual Effects

Testosterone, acting at multiple sites to maintain sexual activity, enhances sexual interest and libido in addition to its local effects on erectile function. It was previously thought that its main action targets sexual interest and libido primarily, but recent data demonstrates local effects for erectile function in respect of expression of NOS in penile tissue which is dependent on androgens. Castration affects PDE5 gene expression, and PDE5i efficacy is seen to be blunted in patients with hypogonadism. Thus, our concept of the pathophysiology of ED has changed, and today we note that testosterone deficiency produces metabolic, structural, and functional alterations in the corpus cavernosum resulting in veno-occlusive dysfunction and explains why PDE5 inhibitors are less effective in ED patients with testosterone deficiency. In animal models, androgen deficiency produces increased accumulation of adipocytes in the sub-tunical region of the corpus cavernosum causing veno-occlusive dysfunction which cannot be restored with PDE5 inhibitors treatment alone.

Mood and General Well-Being

Adequate testosterone is needed for general and mental well-being (data relating mood to serum testosterone divergent). Recent Epidemiologic data showed depressed mood inversely related to bioavailable testosterone. Testosterone replacement in aging men improved general well-being.

Androgens and CVS Diseases

Epidemiologic data showed increased CVS diseases with low serum testosterone levels. Androgen replacement produced a small but significant reduction in HDL cholesterol. Clinical significance of this is unknown. Testosterone has been shown to have direct vasodilatory effects on coronary vessels. Other lipid, coagulation, fibrinolytic, and hormonal factors are changed with use of testosterone.

Central Nervous System

Androgens can affect release of neurotransmitters and modulate neuronal nicotinic receptors. It may interact with acetylcholine binding and thus affect cognition by enhancing hippocampal acetylcholine release and modulating nicotinic acetylcholine receptors. In castrated rats, there is reduced total spontaneous release of acetylcholine.

Thus, serum testosterone correlates with cognitive function and spatial ability in men, and androgen replacement in elderly men improves spatial ability but no effect on memory or verbal fluency.

Bone Mineral Density

When testosterone is split into DHT (dihydrotestosterone) and E2 (estradiol), the E2 maintains good BMD for patients. In hypogonadic males, there is an increased risk of osteopenia and osteoporosis, leading to greater prevalence of femoral neck fractures and compression fractures of the thoracolumbar spine during falls and minor traumata.

Muscle

Testosterone maintains muscle strength and mass and prevents frailty of aging.

Etiopathogenesis of Late-Onset Hypogonadism

Several mechanisms of age-associated decrease in androgen levels have been postulated:

- Primary testicular changes
- Altered neuroendocrine regulation of Leydig cell function
- Increase of SHBG binding capacity
- Decreased adrenal androgen secretion

Primary testicular changes may cause the following:

- Decreased secretary capacity of Leydig cells
- Reduction of number Leydig cells
- Reduction of enzymes
- Shift from $\Delta 5$ to $\Delta 4$ steroids

Fig. 2.3 Declining testosterone with age (Harman et al. 2001)

Altered neuroendocrine regulation of Leydig cell function leads to:

- Modestly and inconsistently higher LH levels
- Slightly increased LH response to GnRH
- Unchanged pulsatile LH secretion
- Diminished frequency of large amplitude LH pulses
- Reduced mean LH pulse amplitude
- Increased responsiveness to negative feedback of androgens
- Decreased hypothalamic GnRH secretion (Figs. 2.3 and 2.4)

Late-Onset Hypogonadism (LOH): Clinical Presentation

In late-onset hypogonadism, the male patient may experience:

- Diminished sense of well-being and energy
- Diminished libido and frequency of intercourse
- Decreased muscle mass and strength
- Increased fat mass + altered distribution
- Decreased skin thickness and male-pattern hair distribution
- Osteopenia/osteoporosis

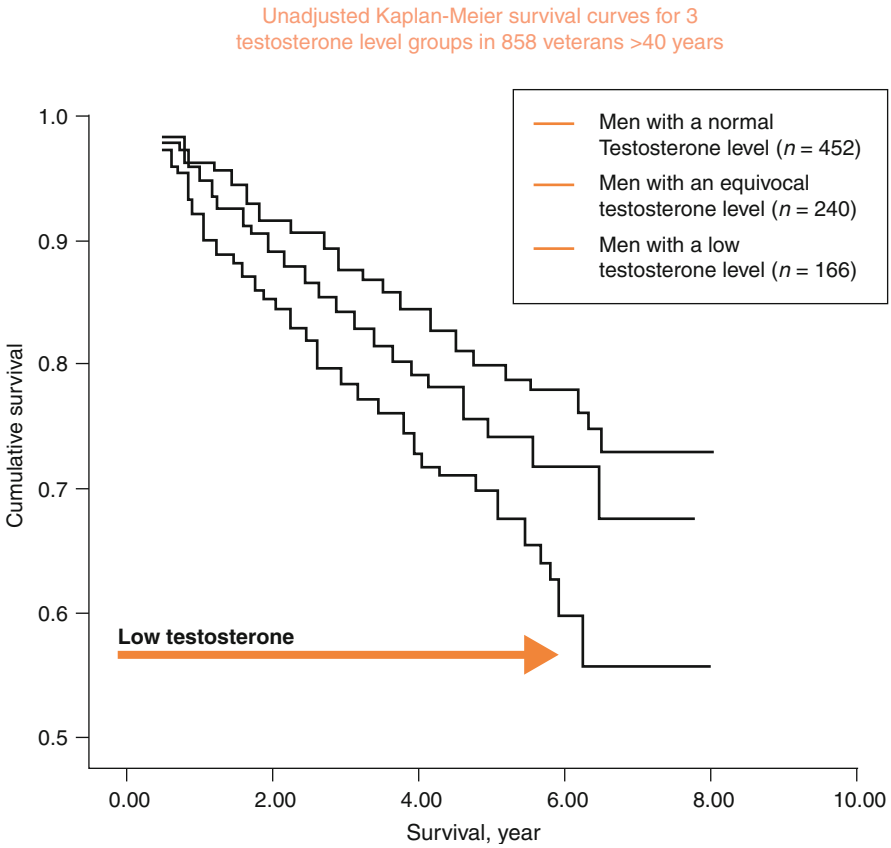

Fig. 2.4 Testosterone levels and survival (Shores et al. 2006)

Benefits of Testosterone Replacement for Men

- Sex drive/potency increase
- Cardiovascular system improvement
- Circulatory system improvement
- Muscular strength improvement
- Cholesterol profile improvement; potential reduction in risk of coronary heart disease
- Leaner body mass
- Improved self-perceived wellness
- Minimization of bone loss
- Stabilization of blood sugar
- Hematological improvement
- Prevention of peripheral vascular disease, muscle cramps, liver dysfunction, Alzheimer's disease
- Improvement of pregangrenous conditions

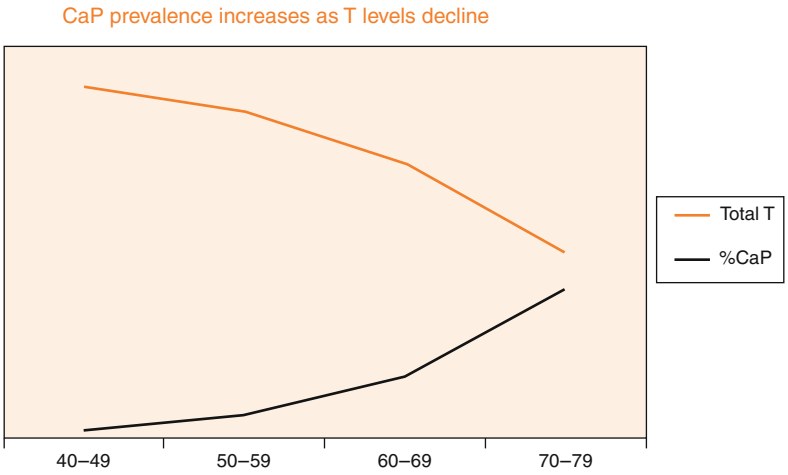

Fig. 2.5 Cancer of the prostate prevalence and testosterone levels

Potential Risks of Replacement Therapy

BPH

- Hypogonadal men have small prostates.
- In hypogonadal men receiving testosterone treatment, prostatic volume increases, but to no greater volume than that of normal age-matched controls.
- PSA levels rise with androgen therapy but should remain within the reference range.
- Maximal increase in volume and PSA occurs by 3 months and does not continue with long-term therapy.

Prostate Carcinoma

- There is no evidence that testosterone treatment causes prostate cancer.
- Testosterone seems to be a "permissive" rather than a "causal" factor.
- This issue is still controversial, but current evidence points to older men with low testosterone being at higher risk of getting carcinoma of the prostate (Fig. 2.5).

Cardiovascular Risk

- Both androgen deficiency and androgen excess are associated with unfavorable lipid profiles and increased CV risk.
- Maintaining androgen levels in the physiological range promotes a favorable lipid profile.

- Early studies have been conducted in hypogonadal men with angina and chronic heart failure showing benefit from normalization of testosterone levels.
- More research is needed on CV risk.

Polycythemia

- Clinically significant polycythemia has been associated with androgen replacement.
- This is more common with conventional injectable (up to 44 %) therapy, where high peak plasma concentrations are found immediately after administration.
- Much less common with transdermal (8 %) therapy or long-acting injection (Nebido).

Liver

- Only alkylated testosterone preparations have been associated with liver disease
- Modern testosterone preparations, either biologically identical testosterone or testosterone esters, are not associated with liver disease.

Other Side Effects

- Other less common side effects are acne, male-pattern hair loss, hirsutism, mood changes, and rarely sleep apnea.

Conclusion

- Decreasing testosterone levels are associated with a decline in:
  - Libido and sexual function
  - Bone mineral density
  - Lean body mass and muscle strength
- Replacement studies in elderly men with *mildly low* testosterone levels have not convincingly shown a benefit or reversal of these changes.
- However, in elderly men with very low testosterone levels (<200–300 ng/dl), there is improvement in libido and BMD and possible improvement in sexual function and the perception of physical well-being.

- Testosterone replacement mildly increases PSA levels and may exacerbate androgen-dependent diseases (BPH and prostate cancer if present and not picked up before starting therapy) which increase with age. However, clinical studies to date are too small to determine any clear adverse effect in the ordinary patient suitable for replacement therapy.
- Testosterone replacement can cause erythrocytosis which therefore mandates a check on the hematocrit during long-term therapy.

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