DISSERTATION

ADULT ONSET MALE HYPOGONADISM:

DIAGNOSIS AND TREATMENT

Submitted by

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ABSTRACT

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Hypogonadism affects an estimated 2–4 million American men with increasing prevalence seen in older men. Normal aging processes lead to decreased biological production of testosterone. However, levels below physiologic function can decrease the quality of life and the life expectancy of men. A clinical diagnosis of hypogonadism, results from this failure to produce testosterone and or normal amounts of sperm and is more commonly referred to as low-Testosterone (low-T). Pharmacologic intervention with exogenous testosterone, hormone replacement therapy, can improve quality of life. However, this intervention is not without risks and should only be done when serum testosterone is below 300 ng/ml and is accompanied with symptoms associated with low testosterone. The aims of this work are to report the most commonly-used clinical symptoms associated with low-T for diagnosis, to provide a list of risks associated with hormone replacement therapy, and to analyze the different forms of pharmacologic intervention known commonly as Testosterone Replacement Therapy (TRT).

Keywords: male hypogonadism, testosterone replacement therapy (TRT), diagnosis, treatment

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DEDICATION

I dedicate this dissertation to Dr. William Hanneman, without his innovative thinking and support this experience would never have been possible. He was ahead of his time working with industry to develop a new type of doctoral student, but was lost too soon. I dedicate this work to Greyson and Ben, for a better future, and to Grandpa Al, who knew I could do anything I set my mind to as long as I had enough time and motivation.

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CHAPTER 1

INTRODUCTION

Hypogonadism in the Context of Male Health

Worldwide, 4–5 million men are affected by hypogonadism (Edelstein & Basaria, 2010) with an estimated 2–4 million of those affected in the United States. The number of men affected by hypogonadism is likely higher than these numbers indicate due to underdiagnosis and under-reporting (Rhoden & Morgentaler, 2004). Hypogonadism is the failure to produce physiological concentrations of testosterone and/or a sperm count >15 million/mL (Basaria, 2014; Jayasena et al., 2022; Salonia et al., 2019; Schlegel et al., 2021). Commonly, the reduction of testosterone is known as low-T. Reduced testosterone can affect men of all ages; testosterone in childhood and adolescence is responsible for the development of external genitalia and secondary sex characteristics (Basaria, 2014; Edelstein & Basaria, 2010). While hypogonadism may not be curable in all males, those diagnosed with hypogonadism do have options for treatment. Testosterone replacement therapy—or TRT—comprises testosterone or testosterone esters that come in a variety of dosage forms, including orals, creams, gels, patches, implants, and injectables (Bhasin et al., 2006).

Role of Testosterone

Testosterone is primarily produced in the Leydig cells of the testes (3–10 mg/day), whereas only 5% of testosterone is produced in the adrenal cortex. Cholesterol serves as the backbone undergoing multiple enzymatic reactions for testosterone synthesis. Testosterone is metabolized into its active metabolite DHT, which has a higher androgen-binding affinity than testosterone. Both T and DHT can bind to the androgen receptor in cytoplasm, this complex

crosses the nuclear membrane to further bind with a hormone-specific receptor, which then modulates the transcription of DNA at androgen receptor (AR) gene. The AR gene is found on the X-chromosome at Xq11-12 (Bielska et al., 2022; Kuiper et al., 1989). Testosterone can also be converted to estradiol by the enzyme aromatase. While aromatase is ubiquitous, it is highly concentrated in adipose tissue.

At the age of 30, men start to experience declining levels of testosterone, reduced Leydig cell sensitivity to LH, and the loss of Leydig cells. These changes are part of the normal aging process (Harman et al., 2001; Neaves et al., 1984; Wang et al., 2017). Some conditions associated with aging—such as bone loss, osteoporosis, increased adiposity, and impaired sexual function—may be associated with the reduction of estrogen, which relies on testosterone as a precursor (Salonia et al., 2019). Testosterone production and spermatogenesis are the two main functions of the testes. Testosterone is synthesized by the Leydig cells and is required for sex differentiation, masculinization, and the process of puberty, along with maintaining the male phenotype (Basaria, 2014).

Role of Hypothalamic–Pituitary–Gonadal Axis

The hypothalamic–pituitary–gonadal (HPG) axis consists of a negative feedback loop where the peptide kisspeptin stimulates hypothalamic neurons in the mediobasal hypothalamus generating the pulsatile release of GnRH. Every 60–90 min, GnRH is released creating and triggering the pulsatile release of luteinizing hormone (LH) and follicle stimulating hormone (FSH) by the anterior pituitary gland into the bloodstream. LH and insulin-like factor 3 work together in the Leydig cells to synthesize testosterone while spermatogenesis is stimulated by the action of FSH and intratesticular testosterone on the Sertoli cells and seminiferous tubules. Sertoli cell hormones, anti-Müllerian hormone (AMH), and Inhibin B, aid in maintaining

masculinization (Salonia et al., 2019). Concentrations of serum testosterone peak in the morning with concentrations ranging from 3–10 ng/mL, which is associated with the 3–10 mg of testosterone the testes produce daily. Testosterone has two major metabolites, dihydrotestosterone (DHT) and estradiol, each synthesized by the enzymes 5-α reductase and aromatase, respectively. Testosterone by way of estradiol suppresses gonadotropin secretion using a negative feedback to the hypothalamus and pituitary (Basaria, 2014).

Background on Hypogonadism

Hypogonadism is defined as either primary or secondary, though new classifications based on age and related pathology are currently being discussed in the literature (Grossmann & Matsumoto, 2017; Salonia et al., 2019). Primary hypogonadism is associated with a disorder of the testes and causes decreased testosterone production (Bhasin & Basaria, 2011). Primary hypogonadism, or *hypergonadotropic hypogonadism*, is characterized by elevated levels of gonadotropin (e.g. luteinizing hormone [LH] and follicle-stimulating hormone [FSH]), significantly low androgen levels (with LH in the general range of 0.8 to 7.6 mIU/mL and FSH in the general range of 1.0 to 20 mIU/mL), and spermatogenesis impairment (Basaria, 2014; Lanser et al., 2021; Pinsky & Hellstrom, 2010; Schlegel et al., 2021). The LH and FSH ranges will vary depending on the assay and the laboratories' historical reference ranges. Secondary hypogonadism is caused by a dysfunction of the HPG axis and is associated with low testosterone production (<300 ng/dL) and low-normal LH and FSH levels (1.0–7.6 mIU/mL; Schlegel et al., 2021; Schoor et al., 2002). The feedback mechanism for the HPG axis is presented in Figure 1.

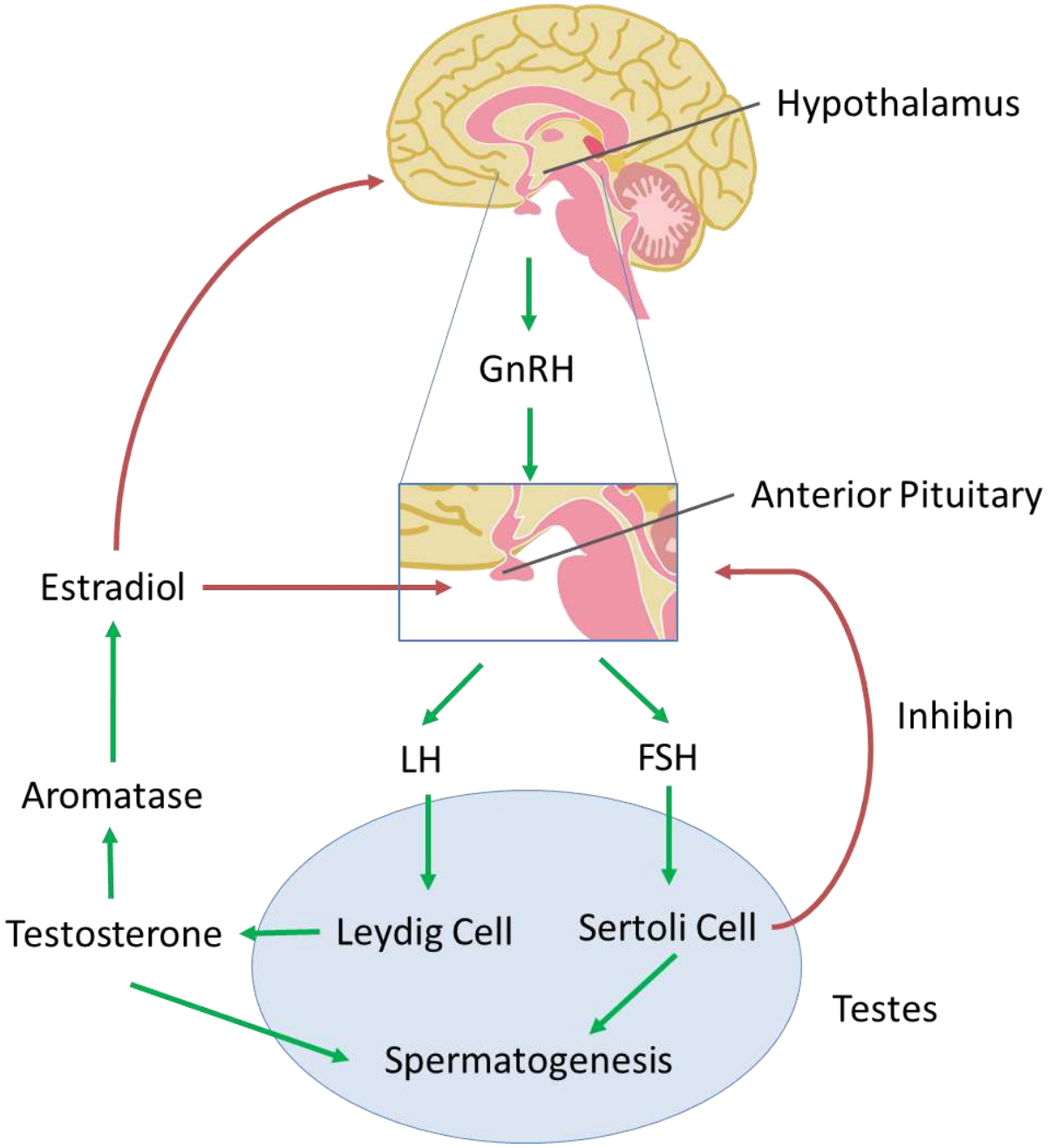

Figure 1. *Hypothalamic-Pituitary-Gonadal Axis*

Note: The green arrows represent positive feedback or stimulation of the HPG axis. The red arrows represent negative feedback or inhibition of the HPG axis. The insert is a close-up of the anterior pituitary. Image created using, in part, the Open Clipart site https://openclipart.org/share.

Hypogonadism can present differently in various age groups. Healthy male children naturally have low testosterone with the lack of spermatogenesis due to the pre-pubertal stage; however, the Sertoli cells are active at this stage and produce anti-Mullerian hormone (AMH). It is possible to diagnose hypogonadism in prepubertal boys based on low concentrations of AMH and inhibin B (Grinspon et al., 2011; Salonia et al., 2019). Generally, hypogonadism is diagnosed during puberty onset, and is part of a diagnosis of delayed puberty. Moreover, delayed puberty diagnosis has an occurrence of < 2% in males 14 years of age or older in the United States (Maggi & Buvat, 2013; Salonia et al., 2019). In fact, this estimate is likely low as other causes, such as transient forms (e.g., constitutional delay of growth and puberty or congenital isolated secondary hypogonadism that may be reversible), are underdiagnosed. In the aging population, hypogonadism may be caused by potentially reversible conditions or be permanent. It is important that practitioners perform a thorough physical exam and have a complete medical history.

Study Objectives

The pathology of hypogonadism determines treatment methods and is imperative to clinical evaluation so that appropriate therapy can be given. Since 2000, there has been a steady increase in the number of men world-wide seeking pharmaceutical intervention for low-T in the aging population, but also among males 15–39 years of age. It is unclear if this increase in pharmaceutical intervention is representative of an increase in androgen-deficiencies, an increase in obesity—which is associated with reduced testosterone levels, or an increase in awareness of symptoms associated with low-T, which in turn is causing an increase in treatment-seeking by patients (Kresch et al., 2021; Layton et al., 2014; Tajar et al., 2012). Testosterone production gradually decreases in aging men and is linked to symptoms commonly associated with aging; it

is likely that as the aging population increases, the diagnosis of low-T and subsequent pharmacologic intervention will also increase. Therefore, the aims of this review include discussing the many clinical symptoms associated with low-T diagnosis, and the risks and benefits of the different treatment methods. In addition, this paper will present a substantial literature review regarding the condition of hypogonadism as well as its diagnosis and treatment.

CHAPTER 2

LITERATURE REVIEW

This chapter will examine the literature on the two main types of hypogonadism as well as on another category, late-onset hypogonadism (LOH). Although the latter is generally considered to be a type of primary hypogonadism, its unique characteristics require that it be explored in-depth and independently, as will occur in the section following that on primary hypogonadism.

Types of Hypogonadism

Primary Hypogonadism

As stated in Chapter 1, primary hypogonadism occurs when there is a dysfunction of the testes, where serum testosterone concentrations are lowered with spermatogenesis impairment causing nonreversible infertility. In addition, gonadotropins are elevated indicating testicular disease in hypergonadotropic hypogonadism (Basaria, 2014). Common causes of primary hypogonadism include: Klinefelter syndrome, chemotherapy and radiation treatments for cancer, and mumps orchitis (Bhasin & Basaria, 2011). In addition, primary hypogonadism has a four times higher incidence in those with Type 2 diabetes and metabolic syndrome; however, the relationship, if any exists, has not been determined (Bojesen et al., 2006; Dahlqvist & Vissing, 2017).

Congenital Causes

Klinefelter syndrome can be caused by a trisomy of 47, XXY or mosaic 46XY/ 47, XXY and is the most diagnosed form of congenital primary hypogonadism in male children, with an incidence of 0.1–0.2% of Klinefelter syndrome in male neonates (Nieschlag, 2013; Salonia et al.,

2019). Klinefelter syndrome is still highly underdiagnosed, but diagnosis is on the rise due to prenatal testing and karyotyping, which looks for chromosomal anomalies. Klinefelter syndrome is the most common form of primary hypogonadism as well as chromosomal aneuploidy and typical phenotypes include: seminiferous tubule atrophy after puberty, spermatogenesis disruption, and small testes. In the initial life stages, Leydig cell function may remain. As the male ages, gynecomastia, tall stature, behavioral issues (e.g., impulsivity, aggression), cognitive, and language skills development issues (e.g., dyslexia), may arise. Diagnosis rates are low, with only 10% diagnosed prior to puberty and 25% never diagnosed. Treatment is required but timing has recently been called into question. There is discussion that treatment should start when testosterone levels are below 300 ng/dL, when clinical symptoms occur, and/or in early puberty when gonadotropin levels increase to aid in full secondary sexual characteristic development and bone health (Groth et al., 2013; Jayasena et al., 2022). In adult males with Klinefelter syndrome, infertility caused by the additional X chromosome of the trisomy condition leads to degradation of the seminiferous tubules and negative effects on Leydig and Sertoli cells leading to impairment of spermatogenesis (Aksglaede et al. 2006; Hawksworth et al. 2018). These effects are more likely to be the cause of infertility than are low testosterone concentrations. The damage to the seminiferous tubules is generally nonreversible; men facing these infertility challenges can consider donor sperm, assisted reproduction technologies, and/or adoption (Basaria, 2014).

Cryptorchidism is another highly recognized condition and involves one (or both) of the testis failing to descend at birth. If the testicle does not descend on its own, which is the norm, it is recommended that surgical intervention take place at age 6–12 months if the testis remains in the abdomen or inguinal areas. The delay in descending can cause issues because testes that

remain in the abdomen or inguinal cavity are exposed to higher temperatures than they would be had they descended into the scrotum, which can in turn reduce testicular function. The incidence of cryptorchidism has been increasing and it is speculated endocrine disruptors may be a cause (Jayasena et al., 2022). Virtanen and Adamsson (2012) found positive associations of cryptorchidism diagnosis with prenatal exposure to estrogen compound diethylstilbestrol (DES) and epidemiological studies suggest an association with phthalates, flame-retardants, dioxins, (PCBs), and pesticide concentrations in breast milk.

Acquired Causes

Acquired primary hypogonadism arises from trauma, serious infection/inflammation (e.g. mumps orchitis), medication, surgery, or treatments for cancer (e.g. chemotherapy or radiation). Typically, orchitis is unilateral and in such cases, 75% of patients retain fertility; in cases of bilateral orchitis, which occurs far less often, a third of patients regain fertility (Jayasena et al., 2022). In cases where azoospermia, no measurable sperm counts in ejaculate, is found to have been caused by chemotherapy, it may be reversible over time based on the duration and dose of the chemotherapeutic agent; however, infertility is still possible and should be discussed with the patient. Alkylating agents have been found to cause mutations and infertility in more than 60% of men treated with chemotherapy (Okada & Fujisawa, 2019; Pinsky & Hellstrom, 2010). In addition, some primary hypogonadal patients may have normal testosterone levels but have decreased bioavailability due to an increase in estradiol synthesis and binding to SHBG; this is usually seen when LH and FSH levels are increased (Pinsky & Hellstrom, 2010). Table 1 presents information and descriptions on the different types of primary hypogonadism. As with adults, children can acquire primary hypogonadism after chemotherapy, radiotherapy, or infection. In ~10% of these cases, secondary sexual characteristics may develop normally if the

cause of the primary hypogonadism occurs prior to puberty; however, onset after puberty can create more permanent effects.

Table 1

Causes of Primary Hypogonadism

Indication	Description	Reference
Congenital Cause		
Klinefelter syndrome [a]	Most frequent sex chromosomal disorder (47, XXY) occurring in 150 per 100,000 males. Presents most often with small testes, gynecomastia, cognitive issues, language skills development difficulties, and infertility. Confirm diagnosis with karyotyping.	(Bojesen et al., 2006; Groth et al., 2013; Salonia et al., 2019)
Cryptorchidism [a]	Condition where one or both testes fails to descend; should be surgically corrected in the first 6-12 months of life to preserve function.	(Jayasena et al., 2022; Salonia et al., 2019)
Y chromosome microdeletion [a]	Gene deletions in the male-specific region of the Y-chromosome.	(Akinsal et al., 2018; Basaria, 2014; Rabinowitz et al., 2021; Salonia et al., 2019)
Acquired Cause		
Mumps orchitis [a]	Inflammation and pain in the testes caused by the mumps virus, which may be unilateral (common) or bilateral (rare); may negatively affect fertility.	(Salonia et al., 2019; Wu et al., 2021)
Medication (glucocorticoids, ketoconazole) [b]	Glucocorticoids at supraphysiological levels inhibit GnRH synthesis. Ketoconazole inhibits CYP17 which is an enzyme needed for androgen synthesis.	(Basaria, 2014; Salonia et al., 2019; Vasaitis et al., 2011)
Varicocele [a]	Enlargement of veins in the scrotum; may negatively affect spermatogenesis and testosterone production.	(Basaria, 2014)
Testicular trauma/torsion [a]	Due to their exposed location, the testes are predisposed to trauma that can lead to atrophy and loss of blood perfusion. Surgery within 6–8 hr of event/onset may preserve viability.	(Basaria, 2014; Jayasena et al., 2022; Salonia et al., 2019)
Chemotherapy/ Radiation [a]	Alkylating agents cause toxic effects in the seminiferous tubules harming the germinal epithelium. Infertility may be reversible if spermatogonia (stem cells) are viable.	(Basaria, 2014; Jayasena et al., 2022; Salonia et al., 2019)

[a] Organic origin
[b] Functional origin

Late-Onset Hypogonadism

Late-onset hypogonadism is where testosterone decreases due to aging; it has historically been referred to as male menopause, “manopause,” andropause, and androgen deficiency syndrome. LOH has recently been classified as a subset of primary hypogonadism by the Endocrine Society, but other literature categorizes it as a combination of primary and secondary hypogonadism. The Endocrine Society is a network of physicians and scientists who specialize in endocrinology that makes policy recommendations to federal agencies and policy makers worldwide (Endocrine Society, 2022). LOH is caused by the aging process, a decrease in the hypothalamic–pituitary–gonadal (HPG) axis function, and loss of Leydig cell function (Bhasin et al., 2018; Dudek et al., 2017; Nieschlag, 2020). Three criteria for diagnosis were established by the European Male Ageing Study (EMAS; Lee et al., 2009), a study that recruited men 40–79 years old in eight major cities in the European countries of Belgium, Estonia, Hungary, Italy, Poland, Sweden, the United Kingdom, and Spain to examine male aging. The criteria EMAS developed are: at least three sex-related symptoms (e.g., decreased sexual desire, morning erections, and erectile dysfunction), testosterone levels below 320 ng/dL, and free testosterone < 64 pg/mL. Comorbidities, most notably obesity and stress caused by systemic disease leading to non-gonadal illness where the HPG axis is suppressed, are common in this age group and should be treated (Jayasena et al., 2022; Tajar et al., 2010; Wu et al., 2010). Obesity causes a down-stream effect of low-T by increasing adipose tissue with highly concentrated levels of aromatase which increases testosterone metabolism to estrogen by aromatase, which in turn suppresses the HPG axis and testosterone synthesis. Regardless of the age of the individual, the negative correlation that exists between testosterone levels and the comorbid condition of obesity is a consistent finding. Importantly, in cases where obesity is deemed to be a significant factor,

testosterone levels can recover with lifestyle management through diet and exercise (Camacho et al., 2013; Jayasena et al., 2022; Kelly & Jones, 2015; Tajar et al., 2010).

Generally, most older men maintain gonadal function that does not require TRT; those that require intervention typically are of poor health and have comorbidities (Jayasena et al., 2022). Due to these comorbidities, LOH often goes undiagnosed as symptoms resemble normal aging, such as osteopenia, increased adiposity, decreased muscle mass, fatigue, decreased libido, and decreased cognitive function (Pinsky & Hellstrom, 2010). In addition, LOH may not be treated by physicians due to untreated comorbidities such as obesity (Barbonetti et al., 2020) and the increased "risk of major adverse cardiovascular events (MACE) such as non-fatal myocardial infarction, non-fatal stroke, and cardiovascular death" (Endo Pharmaceuticals, 2021b, p. 7). The Endocrine Society Guidelines (Bhasin et al., 2018), now recommend men > 65 years old that present with symptoms or conditions and that also have consistently low morning T levels be offered TRT on an individual basis (Barbonetti et al., 2020; Dudek et al., 2017). The potential risks and benefits of TRT should be discussed with men expected to live >10 years and in the 55–69 years age range, and these patients should have their prostate specific antigen (PSA) screened prior to and during TRT. Men > 65 years old that routinely present with low morning testosterone should be evaluated on an individual basis for TRT (Bhasin et al., 2018). In the United States, there is currently no TRT approved with an indication for LOH specifically.

Secondary Hypogonadism

Secondary hypogonadism—or central hypogonadism—is the indirect lowering of testosterone caused by dysfunction of the hypothalamic-pituitary unit is present. As with primary hypogonadism, testosterone concentrations are dramatically lower; however, unlike in primary hypogonadism, gonadotropin concentrations are typically normal to low, leading to

hypogonadotropic hypogonadism (Basaria, 2014). In addition, decreased spermatogenesis is observed (Basaria). Men with secondary hypogonadism with an intact pituitary do not face as many challenges with fertility as other hypogonadal men; moreover, fertility may be restored using pulsatile GnRH therapy, or human chorionic gonadotropin (hCG) weekly injections alone or in combination with FSH weekly injections (Mao et al., 2017; Rastrelli et al., 2014; Salonia et al., 2019). Sustained TRT use is contraindicated for men wanting to become fertile as TRT inhibits testosterone production and spermatogenesis by decreasing the HPG axis.

Causes of secondary hypogonadism include Kallmann syndrome, idiopathic hypogonadotropic hypogonadism, hyperprolactinemia, pituitary damage, certain medications, and isolated congenital gonadotropin deficiency (Basaria, 2014; Pinsky & Hellstrom, 2010). Additionally, pituitary neoplasms, genetic disorders of GnRH, and stunted pituitary development are all potential causes of secondary hypogonadism.

Congenital Causes

Congenital secondary hypogonadism can be identified as reduced GnRH and/or gonadotropin levels while the other components of the HPG axis maintains functionality. It is considered rare with only 1 in 4,000–10,000 boys being diagnosed with deficient GnRH and clinically absent or incomplete puberty (lack of fully developed sexual characteristics) with up to 60% of cases being due to Kallmann syndrome (Boehm et al., 2015; Bonomi et al., 2018; Franco et al., 1991; Salonia et al., 2019). The loss of smell—anomia—is a key symptom used for Kallmann sydrome diagnosis. Congenital hypogonadism may present with other hypogonadal phenotypes, including “cryptorchidism with or without micropenis, renal agenesis, hearing loss, midline defects (cleft lip/palate), and skeletal anomalies” that can make diagnosis difficult (Jayasena et al., 2022, p. 203).

Acquired Causes

Acquired secondary hypogonadism is generally diagnosed after puberty and is caused by head and brain trauma, vascular events, metabolic disorders, surgery, radiotherapy, hyperprolactinemia, or as a result of the use of certain drugs (e.g., marijuana, opiates, glucocorticoids, or androgens; Jayasena et al., 2022; Ross & Bhasin, 2016). Supraphysiological androgen levels due to androgen misuse cause depression of the HPG axis leading to testicular atrophy and infertility. The HPG axis can return to normal function after androgen cessation although it can take months to years to normalize with spermatogenesis taking up to 3 years to recover (Christou & Tigas, 2018; Jayasena et al., 2022; Nachtigall et al., 1997; Rasmussen et al., 2021).

Functional Causes

Functional secondary hypogonadism can be caused by physiological stressors, although it is not very common in men; in such cases it is reversible. Stress, a low-fat diet due to athletic training, eating disorders, and hyperprolactinemia (most common), along with opiate use, are some of the most common physiological bases of GnRH suppression. The HPG axis recovers from suppression once the cause of low energy or hyperprolactinemia is removed. Nevertheless, TRT is typically prescribed for functional secondary hypogonadism as it presents similar to permanent hypogonadism, but also in cases where the cause will not or cannot be remedied in the near future, to mitigate symptoms (Aitken et al., 2014; Ajmal et al., 2014; Dwyer et al., 2019; Jayasena et al., 2022). Table 2 presents additional information on the causes of secondary hypogonadism.

Table 2

Causes of Secondary Hypogonadism

Indication	Description	Reference
Congenital Cause		
Idiopathic hypogonadotropic hypogonadism [a]	Any damage to the hypothalamus or pituitary prior to puberty generally caused by infection, radiation exposure, surgery, or hypothalamus or pituitary infarction. These types of infarctions lead to decreased gonadotropins leading to hypogonadism.	(Pinsky & Hellstrom, 2010; Salonia et al., 2019)
Kallmann syndrome [a]	Congenital delay in puberty where patients have a total loss of or reduced sense of smell and midline facial defects due to GnRH-releasing neuron migration to the hypothalamus during embryonic development.	(Pinsky & Hellstrom, 2010; Salonia et al., 2019)
Acquired Cause		
Medications [b]	Glucocorticoids at supraphysiological levels inhibit GnRH synthesis. Opioids suppress the HPG axis by also inhibiting GnRH synthesis.	(Basaria, 2014; Salonia et al., 2019)
Pituitary damage [a]	Damage to the pituitary resulting in gonadotropin deficiency.	(Basaria, 2014; Salonia et al., 2019)
Hyperprolactinemia [a]	Elevated serum prolactin levels that are produced in the anterior pituitary inhibiting GnRH pulsatile secretion.	(De Rosa et al., 2003; Salonia et al., 2019)
Parasellar tumors [a]	Tumors, lesions, compression and destruction of the HPG region caused by space-occupying tumors.	(Jayasena et al., 2022; Salonia et al., 2019)
Chronic illness, malnutrition, obesity [b]	HPG axis physiological suppression	(Jayasena et al., 2022; Salonia et al., 2019)

[a] Organic origin
[b] Functional origin

CHAPTER 3

METHODS OF DIAGNOSIS

Determining the type of hypogonadism is required to distinguish between primary and secondary hypogonadism, and requires further diagnosis to determine etiology. Diagnosis should occur in a step-wise fashion based on reported clinical symptoms with emphasis on pubertal delay, past chemotherapeutics, radiotherapy, orchiectomy, and Klinefelter syndrome. In addition, some symptoms are more correlated to hypogonadism, whereas other symptoms are less specific. While TRT is the primary treatment for secondary hypogonadism, alternative treatments and regimens may be considered when trying to maintain, induce, or restore fertility, including fertilization through microsurgical testicular sperm extraction (mTESE) and assisted reproductive technology (ART), which includes *in vitro* fertilization (Boehm et al., 2015; Hawksworth et al., 2018; Jayasena et al., 2022).

Signs & Symptoms

Hypogonadism is diagnosed by signs and symptoms of deficient androgen concentrations. While most hypogonadal patients have signs and symptoms, not all patients will exhibit decreased libido, sexual function, or even reduced energy levels with low testosterone concentrations (Pinsky & Hellstrom, 2010). Serum testosterone levels peak in the morning due to diurnal circadian rhythm, with decreased testosterone levels observed during the evening (Basaria, 2014). Blood samples should be taken from fasted and well-rested patients from 8 am to 10 am to reduce the occurrence of false-positive results and utilizing repeated samples to determine consistency regarding low-T levels. Measuring testosterone levels at peak concentrations provides a more reliable estimate of biologic levels; therefore, blood samples

should only be taken in the morning soon after rising. Additionally, testosterone levels may be artificially lowered if men are overly tired, non-fasted, ill, or not disclosing prescribed/recreational drugs, leading to a false diagnosis of hypogonadism (Jayasena et al., 2022).

Symptoms associated with hypogonadism can be specific, suggestive of low-T, or can be non-specific with many linked to normal ageing; therefore, confirming low levels of testosterone in blood in the morning is imperative for a proper diagnosis of hypogonadism. Table 3 presents a list of hypogonadal symptoms used for diagnosis of the condition. In addition to the listed symptoms, the medical practitioner should make note of any known genetic abnormalities, such as Kallmann syndrome, whether or not the tone of voice is age appropriate, and the pattern of hair growth as these can indicate incomplete puberty and aid in the diagnosis of hypogonadism.

Table 3

Symptoms of Hypogonadism for Use in Diagnosis

Suggestive of Hypogonadism	Less Specific to Hypogonadism	References
• Decreased libido and sexual activity • Decreased spontaneous erections or erectile dysfunction • Decreased muscle mass • Decreased bone mass or osteoporosis • Infertility • Cryptorchidism • Hot flashes and sweats • Gynecomastia or breast discomfort • Height loss or minimum-trauma fracture • Anemia, reduced hemoglobin or hematocrit without known causes • Decreased testicular volume • Decreased pubic and axillary hair • Decreased frequency of shaving	• Sleep disturbances • Decreased energy and motivation • Difficulties with concentration and memory • Depression or decreases in mental stability • Decrease in metabolic function • Obesity	Behre et al., 1997; Bhasin & Basaria, 2011; Buvat et al., 2013; Corona, Rastrelli et al., 2013; Corona, Vignozzi et al., 2013; Dobs et al., 2014; Jayasena et al., 2022; Layton et al., 2014; McGill et al., 2012; Ramasamy et al., 2014; Rhoden & Morgentaler, 2004; Tartavoulle & Porche, 2012; Vermeulen, 2001; Vigen et al., 2013

Pharmacological intervention should only occur when symptoms are negatively affecting quality of life and when total testosterone is below threshold levels. While both factors are relevant to treatment decisions, the former is critical as it is dangerous for testosterone to reach supraphysiological levels. Levels of testosterone above physiologic norms carry many risks, such as erythrocytosis, gynecomastia, and infertility (Basaria, 2014).

Hypogonadism diagnosis requires low testosterone levels on two or more blood draws to confirm low testosterone levels in addition to signs and symptoms. General health is evaluated along with general signs and symptoms and excluding any acute, subacute, or systemic illness, eating disorders, excessive exercise, or substance abuse/misuse (with particular emphasis on alcohol, marijuana, and opiate usage). If androgen deficiency is detected, LH and FSH levels should be measured, to determine if the dysfunction is related to the testes or the hypothalamic-pituitary unit. Hematocrit (Hct) should be evaluated as well to determine baseline values and aid in screening for other conditions such as anemia or polycythemia where too many blood cells are produced and may lead to blood clots. Due to these factors and issues, Bhasin and Basaria (2011) noted:

> Men with secondary hypogonadism need additional evaluation, including measurements of prolactin levels, other pituitary hormones, serum iron and transferrin saturation, and MRI scan, to exclude hyperprolactinemia, hemochromatosis, and space occupying lesions of the hypothalamus and pituitary; the extent of this additional evaluation should be individualized. (p. 254)

In 2018, the American Urological Association (AUA) suggested testing prolactin levels once low-T levels are confirmed and LH and FSH values have been obtained showing low to low-normal LH, to rule out hyperprolactinemia or other endocrine diseases (Mulhall et al., 2018).

If low testosterone levels are present prior to the end of puberty, the individual may experience "delayed or incomplete sexual development, eunuchoidal proportions ([arm] span greater than height by more than 2 cm), retention of the high pitched voice, and the failure to experience the temporal recession of hair with advancing age" (Bhasin & Basaria, 2011, p. 253). Diagnosis of hypogonadism after puberty typically presents with a lack of adult male characteristics (e.g., lack of facial and body hair, gynecomastia, undersized testes) and other symptoms such as infertility and fewer events of spontaneous erection (Bhasin et al., 2006). Men with gynecomastia and breast tenderness should have estradiol levels measured; if levels are elevated the patient should see an endocrinology specialist as this is uncommon (Mulhall et al., 2018). Another disease associated with hypogonadism is osteoporosis, which can be prevalent in hypogonadal men as estrogen and testosterone are required for bone health. Osteoporosis is caused by osteoclast cell mediated bone resorption when estrogen and testosterone concentrations are low. Osteoblasts maintain bone health by generating bone matrices and aiding in mineralization; these cells are stimulated by estrogen which is converted from testosterone by aromatase (Michael et al., 2005). As previously stated, another issue that complicates diagnosis is that hypogonadal symptoms can be nonspecific. Due to the many comorbidities, such as obesity, that can lower testosterone levels, it is not advised to screen the general public for androgen deficiency. Evaluation for hypogonadism should occur in those with consistent signs and symptoms that have a negative impact on the patients' well-being and lifestyle.

In addition to low testosterone levels, additional parameters should be evaluated. If low-T and low/low-normal LH levels are found, prolactin should be measured. If high prolactin (> 250 ng/mL) with unknown cause is found, further evaluation should be performed to determine the cause (e.g. hypothyroidism and neuroleptics dopamine receptor antagonist drugs; Thapa &

Bhusal, 2021). Prolactin levels are used to screen for hyperprolactinemia potentially indicating a pituitary tumor, it is recommended that the patient be further evaluated by an endocrinologist (Ajmal et al., 2014; Mulhall et al., 2018). Please see Figure 2 for a flowchart regarding the diagnosis and treatment process.

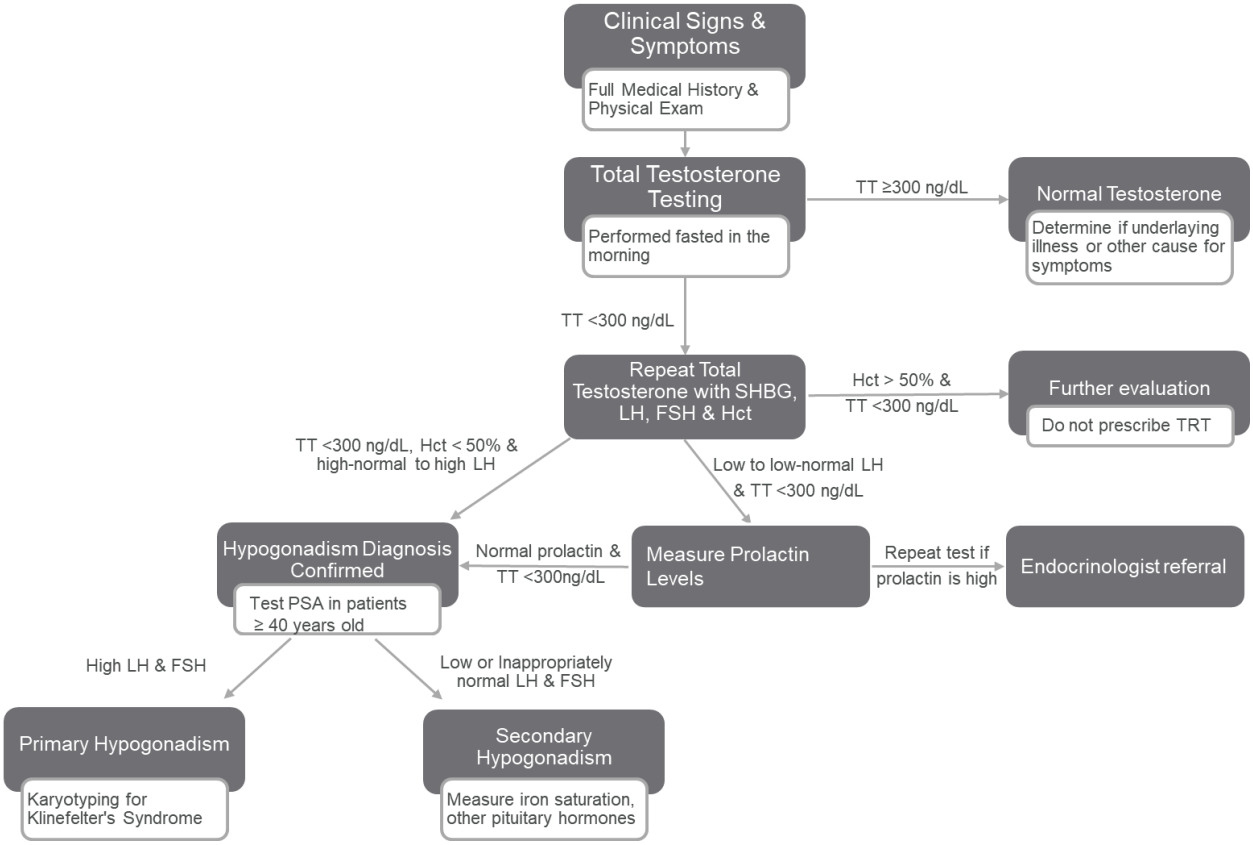

Figure 2. *Male Hypogonadism Diagnosis and Management Flowchart*

Note. TT – total testosterone, Hct – hematocrit, LH – leutinizing hormone, FSH – follicle stimulating hormone, TRT – testosterone replacement therapy, PSA – prostate specific antigen. Adapted from similar flowcharts in Basaria (2014, p. 1253); Bhasin et al. (2006, p. 1999); Jayasena et al. (2022, p. 214); and Mulhall et al. (2018, p. 425).

Use of Testosterone Analysis

Using a reliable assay is imperative. When evaluating testosterone levels, diagnosis should be based on a validated method with historical reference for the lower limit range for healthy young men, this is true of all assays used to diagnosis T-syndromes (Bhasin et al., 2006). A new harmonized reference range for healthy, non-obese men aged 19–39 years was recently published for the 2.5th and 97.5th percentiles of 303 to 852 ng/dL. This reference range was

validated for CDC-certified total testosterone assays as these assays have undergone rigorous testing and reduce variation seen between test methods and bioanalytical laboratories (Travison et al., 2017). The European Endocrine Society uses 200 to 400 ng/dL as the borderline range for low testosterone (Bhasin et al., 2018) while the American Urological Association recommends a lower limit of 300 ng/dL (Mulhall et al., 2018).

Analysis Methods

Quantifying testosterone levels with mass spectrometry produces consistent, reliable, and accurate results (Basaria, 2014). Most laboratories use either a commercial ELISA kit or LC-MS to analyze serum testosterone and SHBG; these values are then used to calculate free testosterone. Historically, LC-MS/MS has been considered the "gold standard" analytical method due to the sensitivity and analyte selectivity of LC-MS/MS; however, immunoassays are commercially available and are being developed to be even more sensitive to male-specific levels of these hormone analytes, which may be lower than an LC-MS/MS can detect. Also, some assays have 4% coefficient of variation (CV) between labs while LC-MS is up to 10% CV, reducing variation and making the immunoassay a more attractive methodology (Jayasena et al., 2022).

Impact of Testosterone Binding

Testosterone is highly bound to other compounds in the body, most notably in the blood; of the total testosterone present, roughly 96–99% of it is not free, meaning not readily available to be used by the body to support male sex characteristics and function. In addition, of the bound testosterone, the majority (60%) is bound to sex hormone binding globulin (SHBG; Pinsky & Hellstrom, 2010). The balance of this non-free testosterone is bound to albumin, a highly prevalent protein which comprises 60% of total serum proteins. However, since it is only

loosely-bound or considered to have low affinity to that protein, the testosterone bound to albumin is considered bioavailable, meaning that under certain circumstances (e.g., passing through capillary beds where it dissociates from albumin) it can be used by the body to support typical function and development. These numbers and percentages become important in the testing and analysis process since many testing procedures measure only total testosterone in the blood and assume that the typical amount—1%–4%—is "free" and do not further test to determine if more or less than typical amounts of testosterone are bound to SHBG, meaning not available (Pinsky & Hellstrom, 2010). If more than typical percentages are being bound to SHBG, due to issues such as aging, hyperthyroidism, high estrogen levels due to liver disease and HIV, this means that the very small amount of free testosterone is reduced and can have a greater impact on the male body's standard function.

Testosterone has the highest binding affinity to SHBG compared to albumin or other proteins found in blood. Bound testosterone levels can change based on physiological and pathological causes, making it difficult to confirm a hypogonadism diagnosis. Patients that have borderline total testosterone levels (200-400 ng/dL) should have free testosterone calculated based on a formula that takes SHBG into account. Multiple such formulas have been developed, with the Vermulean formula being the most-used over the last 20 years. This formula has been validated clinically and was recently validated with state-of-the-art analytical techniques (Fiers et al., 2018; Goldman et al., 2017; Holmboe et al., 2021; Jayasena et al., 2022; Vermeulen et al., 1999).

It should be noted that SHBG levels can vary based on patient health, age, weight, and medications. Aging, hyperthyroidism, hyperestrogenemia, HIV, and some anticonvulsants are known to increase levels of SHBG. Conversely, obesity, insulin resistance, diabetes,

hypothyroidism, glucocorticoids, nephrotic syndrome, and non-alcoholic fatty liver disease can decrease levels of SHBG (Basaria, 2014; del Mar Grasa et al., 2017; Hua et al., 2017).

Testosterone Replacement Therapy

Treatment Determination

Once a diagnosis of hypogonadism is confirmed, the physician may decide on a course of treatment. This should be considered in cases where there has been impact related to secondary sex characteristics (e.g., axillary/pubic body hair reduction), loss of sexual function, and reduction in muscle mass/strength; issues such as a reduction in bone density are also factors that might lead to a recommendation to begin treatment. TRT should also be offered to androgen-deficient men with low libido and erectile dysfunction (ED), in which the origin has been identified (Bhasin et al., 2006). Men with testosterone levels less than 200 ng/dL require treatment, TRT is likely to also benefit men with 200-400 ng/dL testosterone levels, which the Endocrine Society considers the borderline range for low testosterone (Bhasin et al., 2018; Pinsky & Hellstrom, 2010). Prior to starting TRT, a baseline hematocrit and hemoglobin should be established as TRT can increase Hct and thereby increase the risk of polycythemia. During treatment, if Hct is ≥ 54%, reducing the dosage or temporarily discontinuing TRT is recommended. Also, prostate-specific antigen (PSA) should be evaluated in patients over 40 to exclude those with occult prostate cancer. The AUA recommends men on TRT should receive the lowest dosage required to achieve a normal physiological range of 450–600 ng/dL and symptom relief. If symptom relief is not achieved in this range or T levels remain deficient, TRT should be discontinued. If patients achieve T levels in the range of 450-600 ng/dL but do not obtain symptom relief, TRT should be discontinued after 3–6 months of treatment, which is considered a reasonable time period over which symptom relief, if possible, can be achieved.

Further evaluation should occur to determine if another etiology is responsible for symptoms (Mulhall et al., 2018).

Not all men with low androgen levels should be placed on TRT; when low androgen has been identified TRT should only be offered on an individual basis. Short-term treatment should be considered for patients who need to maintain or increase lean body mass, bone density, and strength, such as those who are HIV+ and patients on a regimen of high glucocorticoids (Bhasin et al., 2006; Bhasin et al., 2018). Increased concerns around abuse, myocardial infarction, and prostate cancer have diminished the use of TRT, as many men did not meet established guidelines for treatment. This increase in prescriber worry could keep hypogonadal men that require treatment from receiving life-changing therapy (Rotker, 2020). Some of these concerns on the part of physicians have been addressed by the variety of TRT-delivery methods that have been approved by the FDA, including: topical gels, transdermal patches, nasal delivery, oral pills, intramuscular and subcutaneous injections, and surgical pellet implants (Kresch et al., 2021; Yassin & Haffejee, 2007).

TRT methods have been modified to provide a safer, more patient-centered and patient-compliant experience. Drug manufacturers have introduced changes to the route/method of administration, made structural changes to the testosterone molecule via esterification allowing for reduced dosing with injectable products and oral administration, and combinations of treatments also have been explored (Yassin & Haffejee, 2007). A specific scenario would be that of testosterone gels that can be transferred when an individual touches the treated area and then touches someone else, such as a child. This particular risk has been offset through the development of injectables for cases where accidental transfer is a danger, to eliminate this possibility.

Treatment options for those hoping to maintain fertility include a few that do not include exogenous testosterone. These options work to limit the negative feedback by estrogen, such as selective estrogen receptor modulators (SERMs), aromatase-inhibitors, and human chorionic gonadotropin (hCG). However, testicular function is needed for these treatments to work (Kresch et al., 2021). The method and type of TRT utilized should be determined with the patients' dosing needs in mind in addition to pharmacokinetics, route of administration, and cost (Bhasin et al., 2006).

Testosterone Chemical Modifications

Testosterone has a variable half-life of 10 to 30 min creating difficulties around dosing regimens with peaks and troughs in the supra- and super-physiological levels (Barbonetti et al., 2020; Kresch et al., 2021; Veldhuis et al., 2010). In addition, orally administered testosterone is well-absorbed in the intestines, but undergoes rapid and extensive first-pass metabolism in the liver inactivating and greatly reducing the level of systemic testosterone (Basaria, 2014; Edelstein, 2021). Modifications to the testosterone structure have been explored to increase half-life thereby decreasing peak/trough extremes and decreasing the number of required doses or to alter gastric metabolism and aid in bypassing first-pass metabolism. Testosterone modifications at the 17α-position and 17β-position have been performed, with the 17β-position being preferred. The addition of an ester with a long carbon-chain at the 17β-position slows the metabolism of testosterone by introducing a carbon chain that undergoes hydrolysis prior to metabolism of the parent compound, testosterone. The addition of a methyl group at the 17α-position prevents liver metabolism and binds with receptors; however, prolonged use can lead to liver damage known as hepatotoxicity, and standard bioanalytical assays cannot detect this type of modified testosterone. This makes diagnosis and routine testosterone level checks difficult. There are approved 17α-

position treatment options available; however, they are not generally prescribed due to the known hepatotoxicity (Bhasin & Basaria 2011; Kalinchenko et al. 2017).

Topical Products

Transdermal TRT options reach systemic circulation by penetrating the skin and avoiding first-pass metabolism in the liver. Transdermal options include patches and gels, which use alcohol-based excipients or penetration enhancers that allow testosterone to pass through the stratum corneum and reach systemic circulation (Kresch et al., 2021). Topical gels are generally alcohol-based and should be applied to clean skin at one or more sites on the arms, shoulders, or thighs—depending on the medication—in the morning; patches should be applied at night and placed on the back, abdomen, upper arm, or thigh. Topical gels and patches should not be applied to genitals. Absorption is relatively quick and occurs within 5–10 min; physiological ranges are reached within 2–4 hr after application and full absorption is typically achieved after 6 hr. The use of a moisturizing cream may be needed as testosterone gels can cause dryness and irritation, although they are well-tolerated by most patients. Gel formulations can be transferred by skin-to-skin contact so it is advised to wash hands thoroughly and wear clothing over the completely dry application site (e.g., arm, shoulder, thigh; Cunningham et al., 2017; Jayasena et al., 2022; Wang et al., 2000). Currently there is one FDA-approved branded testosterone patch and multiple branded testosterone gel formulations.

The Androderm® patch consists of testosterone in a hydroalcoholic gel with dosage strengths of 2 and 4 mg testosterone. One 4 mg patch applied at night is the recommended starting dose. Patches are placed on the arm, thigh, or centrally on the back or abdomen. Dosage should be adjusted based on side effects and testosterone levels at 2 weeks after starting

treatment. It takes 8 hr for maximum testosterone concentrations to be reached with a half-life of 70 min (Allergan Inc., 2020).

AndroGel® 1.62% is a hydroalcoholic gel containing testosterone that is available in a metered pump. This concentrated formulation should only be applied to the shoulders and has 20.25 mg testosterone per pump. The recommended starting dose is 40.5 mg testosterone, with dose ranges of 20.25 to 81 mg testosterone. Testosterone levels should be evaluated 14 and 28 days after treatment is initiated or after any dosage adjustment (AbbVie Inc., 2020; Kresch et al., 2021).

Testim® 1% is another testosterone gel formulation containing the penetration-enhancer pentadecalactone (Liu et al., 2011). Testim is available in 50 mg tubes with a recommended starting dose of 50 mg testosterone daily. Like Androgel, peak testosterone levels are reached in 4 hr when applied to the shoulders with a maximum dose of 100 mg testosterone, if needed. Testosterone levels should be checked 2 weeks after treatment is initiated. Endo Pharmaceuticals, the maker of Testim, also has a 2% gel listed under the brand name Fortesta® that includes the penetration enhancer oleic acid. Fortesta delivers 10 mg testosterone per metered pump actuation with a recommended starting dose of 40 mg testosterone that is to be applied to the front and inner thighs. This formulation is more concentrated than the other gels, allowing for more precise dosing. The dose can be increased or decreased in increments of 10 mg testosterone to achieve physiological levels. Testosterone levels should be checked at 2 hours after application, when maximum concentrations are reached. Subsequently, testosterone levels should be tested 2 hours after application at 14 and 35 days after treatment is started to confirm physiological testosterone levels or determine if dose adjustment is required (Endo Pharmaceuticals Inc., 2021(b), 2022).

Vogelxo® 1% gel formulation contains three different penetration enhancers in unit dose tubes, packets, or a metered pump. Titration ranges from 50 mg (starting dose) up to 100 mg testosterone and should be applied to the upper arms where the application site can be covered by clothing (Upsher-Smith Laboratories LLC, 2020).

Injectable Formulations

Injectable forms of TRT contain testosterone that has been chemically modified at the 17β-position with the addition of an ester to provide a consistent release of testosterone with an increased duration of effect. The constant release of testosterone eliminates the endogenous diurnal pattern of testosterone, which is required for spermatogenesis. The consistent release of testosterone is not problematic in hypogonadal men; however, men wanting to maintain fertility should seek other treatment options (Yassin & Haffejee, 2007). In addition, 17β-position modifications using undecanoic acid can be administered orally as testosterone undecanoate (TU) is taken into the intestinal lymphatic system, in this way bypassing first-pass metabolism by the liver (Horst et al., 1976; Shackleford et al., 2003).

The addition of an ester at the 17β-hydroxyl position is responsible for the extended release of testosterone; the half-life increases due to the length of the side chains and the change in the hydrophobicity of the molecule (Bhasin & Basaria, 2011); solubility of testosterone in oil is also increased by the addition of the side chain (Barbonetti et al., 2020). Testosterone esters are rapidly de-esterified in blood; esterification of testosterone creates a more hydrophobic molecule reducing release from the injection site into systemic circulation. Testosterone undecanoate, one of the more recently approved esters, follows the same metabolic pathway as other esters with its 11-carbon chain; testosterone cypionate, enanthate, and propionate have 9, 7, and 3 carbons, respectively (Edelstein & Basaria, 2010). Shorter-acting testosterone and

testosterone ester injectable formulations lasting 1–4 weeks can be less desirable than longer-acting injectable formulations providing effect for 10 weeks or more due to testosterone variability creating supra- and infra-physiological levels of testosterone (Pinsky & Hellstrom, 2010).

TRTs containing oils are the most commonly-used forms of therapy due to their high rate of patient compliance and ease of use (Middleton et al., 2015). Generally administered in the gluteal or upper thigh, off-label use has shown improved pharmacokinetics and injection site tolerability when given SC. In addition, patients have been found to prefer the SC route over the IM and dermal routes (Spratt et al., 2017). Depending on the oil formulation of testosterone ester, testosterone levels quickly peak and trail-off over time. Some patients, those usually on short-acting testosterone esters, may experience symptoms based on these peaks and troughs, such as mood swings, varying energy levels, and variations in sexual interest. Oil formulations can be given IM or SC with IM preferred for lipophilic drugs, like testosterone and testosterone esters, as they absorb faster due to greater muscle vasculature and because a larger injection volume can be administered. The more lipophilic the drug, the slower the drug is released from the oil. O'Brien et al. (2021) examined fractionated coconut oil, castor oil, and sesame oil injected IM versus delivered SC using a pig model and found that the half-lives were 14 days, 20 days, and 23 days, respectively, indicating oils are retained at the injection site and lipophilic drugs will likely be retained longer as well.

Current preparations of testosterone cypionate (TC) are formulated in cottonseed oil and injected IM under the brand name Depo®-Testosterone or as a generic. Recommended starting dosages are 50–400 mg every 2-4 weeks; alternative dosing has been recommended of 75–100

mg weekly or 150–200 mg every 2 weeks in the Endocrine Society Clinical Practice Guidelines (Bhasin et al., 2018; Kresch et al., 2021; Pharmacia and Upjohn Company LLC, 2020).

Testosterone enanthate (TE) is available as an intramuscular injection or can be injected subcutaneously using an auto-injector under the brand name Xyosted®. The IM generic treatment regimen is similar to the TC protocols recommended by the Endocrine Society. Xyosted, however, is offered in three pre-filled auto-injector dosages of 50 mg, 75 mg, and 100 mg in 0.5 mL sesame oil with a starting dose of 75 mg to be injected into the abdomen weekly (Antares Pharma Inc., 2021; Kresch et al., 2021).

Testosterone undecanoate (TU), which is found in Aveed, is the longest-acting testosterone ester. One month after the first Aveed injection, a loading dose is administered, then dosing is done every 10 weeks. While Aveed is the longest acting, it also has one of the largest injection volumes at 3 mL deep gluteal injection. Unlike other TRT options, there are no dose titrations. Aveed also is a part of a Risk Evaluation and Mitigation Strategy (REMS) program due to the chance of developing pulmonary oil microembolism (POME) associated with the castor oil in the formulation and/or anaphylaxis after administration due to the formulation benzyl benzoate (Endo Pharmaceuticals Inc., 2021(a); Ong et al., 2012). When compared to other testosterone esters, TU had the slowest increase to maximum concentrations of 7 days (compared to TE's 1–2 days), and a half-life of 18–24 days (compared to the 4.5 days of TE; Kaminetsky et al., 2019; Kresch et al., 2021; Zhang et al., 1998).

In a study conducted by Middleton et al. (2015), injectable TRT options administered by experienced nurses were evaluated in patients with non-andropause hypogonadism for approximately 3.5 years to compare clinical trial observations to routine clinical practice injection complications and observations. Evaluations were made using 1000 mg/4 mL TU in oil,

with formulations administered over 2 min. They found that post-market and clinical trial data submitted to the agency varied from the study's findings. These findings concluded that the clinical trial data:

> Discounted 97% (107 of 110 reports in 102 men) of putative POME reports with 23 regarded as 'intermediate' and 84 as not POME. No specific definition of 'intermediate' cases was provided, but if the 'intermediate' cases were included the rate of POME is comparable with our findings (13 vs 19/1000 injections). (Middleton, 2015, p. 514)

Due to this definition, POME is considered a rare adverse event. In the clinic, 2% of injections resulted in patients experiencing POME, which typically occurred immediately after injection and lasted up to 10 min, with a mean time of 3 min and without the need for supplemental oxygen. In addition, reoccurrence of POME in patients was greater than expected or by random occurrence. It is speculated this is due to the oil's ability to reach the venous system where the oil can be taken up in the lymphatic system. The authors did not find correlation to age, underlying disease, or injector. A common side effect of 1000 mg/4 mL TU in oil is mild polycythemia, which can be managed by reducing the dosing frequency (Middleton et al., 2015).

Pellet Implants

Testosterone pellets were one of the first approved TRTs in 1972. Testopel® (Endo Pharmaceuticals Inc., 2018) is made of 75 mg testosterone compressed with stearic acid NF and polyvinylpyrrolidone USP to form a cylindrical pellet that is 3.2 mm in diameter and 9 mm in length. The pellets require an outpatient visit as a small incision is required to place the pellets subcutaneously along the beltline. General dosing is 150–450 mg testosterone implanted every 3–6 months with a half-life of 2.5 months (Endo Pharmaceuticals Inc., 2018; Handelsman et al., 1990). Based on clinical studies and provider-prescribed doses, higher doses are typically

required to achieve results (Kresch et al., 2021; McCullough, 2014) with pellet extrusion being one of the major side effects. Reformulation of the pellets using newer technologies decreased the number of extrusion events (Pinsky & Hellstrom, 2010).

Nasal Gel

Natesto® is a nasal gel with 5.5 mg testosterone per actuation that comes in a metered actuation pump. Natesto is delivered by one actuation per nostril every 6–8 hr for a total dose of 33 mg testosterone per day. Testosterone levels should be checked 4 weeks after the initial dose. Peak levels of testosterone are reached within 40 min as testosterone is absorbed by the mucosal membranes into systemic circulation bypassing first-pass metabolism in the liver. Treatment with Natesto may restore HPG axis function due to Natesto's short-acting formulation by mimicking the pulsatile nature of HPG hormones (Kresch et al., 2021; Masterson et al., 2018). Side effects may include nasopharyngitis, rhinorrhea, epistaxis, and upper respiratory infection. This is a unique TRT option as spermatogenesis can be maintained due to the peaks/troughs that mimic the normal diurnal pattern of testosterone in young healthy males.

Oral Forms

Oral testosterone formulations have come a long way recently with the approval of Jatenzo® TU as the active pharmaceutical ingredient. An oral option reduces the risk of transference and of pain upon injection. Jatenzo has developed a self-emulsifying formulation that reduces the need for regimented dosing around meals as oral testosterone formulations are heavily dependent on fat content to be absorbed (Kresch et al., 2021). Jatenzo has decreased absorption during fasting or meals containing < 10% fat but shows consistent absorption with typical Western diets containing ~30% fat (Yin et al., 2012). Testosterone levels peak 4 hr after dosing of 237 mg when taken twice daily with food. Doses range from 158 mg–396 mg twice

daily after titration has been established (Clarus Therapeutics Inc., 2021). Jatenzo has been reported to cause nausea, diarrhea, and burping. Table 4 presents a list of approved testosterone treatment options and delivery methods.

Table 4

Comprehensive Presentation of TRT Treatment Options

Administration Route	Product Name/Mfr.	Dose (mg)	Duration	Black Box Warning	Patient Population	Advantages	Disadvantages
Testosterone							
Topical	Androderm® 2 and 4 mg per patch [a] Allergan, 2020	Starting dose of one 4 mg patch applied at night to the back, abdomen, upper arm, or thigh, then titrated based on T levels 2 weeks after starting treatment or following dose adjustment.	Daily	None	18 and up; not for late-onset hypogonadism	Easy to titrate, reduced peaks and troughs, can mimic natural diurnal T cycle, no injection pain. Quick and easily applied.	Can cause skin irritation. Proper patch disposal critical to reduce chance of T exposure thru handling.
	AndroGel® 1.62% 20.25 mg metered pump actuation [a] AbbVie, 2020	Starting dose of 4.5 mg (2 pump actuations) applied to the shoulders and upper arms in the morning; titration based on pre-dose morning T levels 14 and 28 days after starting treatment or following dose adjustment	Daily	Yes - transference (secondary exposure to children causing virilization)	18 and up; not for late-onset hypogonadism	Topical gels are easy to apply with flexible dosing regimens and dosing titrations. Topicals have good dermal tolerance with reduced-to-no peaks and troughs between applications. No pain on injection.	Potential for transference. May cause dryness and irritation; potential transference. Takes time to apply. Increased DHT levels due to 5α-reductase present in skin. Dose titration needs to be monitored closely due to large inter- & intra-individual T levels.
	Testim® 1% 50 mg tube [a] Endo Pharmaceuticals, 2021(b)	Starting dose of 50 mg (one tube) applied to clean, dry, skin of the shoulders and/or upper arms, preferably in the mornings, titration based on pre-dose morning T-levels 14 days after treatment start or following dose adjustment	Daily	Yes - transference (secondary exposure to children causing virilization)	18 and up; not for late-onset hypogonadism		

Administration Route	Product Name/Mfr.	Dose (mg)	Duration	Black Box Warning	Patient Population	Advantages	Disadvantages
Topical, cont.	Fortesta® 2% 10 mg metered pump actuation [a] Endo Pharmaceuticals 2022	Starting dose of 40 mg (4 pump actuations) applied to the thighs in the morning; titration based on pre-dose morning T-levels 14 and 35 days after treatment start or following dose adjustment	Daily	Yes - transference (secondary exposure to children causing virilization)	18 and up; not for late-onset hypogonadism		
	Vogelxo® 1% 50 mg tube, 50 mg packet &12.5 mg per metered pump actuation [a] Upsher-Smith Laboratories, 2020	Starting dose of 50 mg (one tube, one packet or 4 pumps) applied to the shoulders and/or upper arms, titration based on pre-dose morning T-levels 14 days after treatment start or following dose adjustment	Daily	Yes - transference (secondary exposure to children causing virilization)	18 and up; not for late-onset hypogonadism		
Subcutaneous Implant	Testopel® 75 mg per pellet [a] Endo Pharmaceuticals, 2018	Starting dose 150–450 mg SQ every 3–6 mo. Dose can be based on testosterone propionate dosage, if known. To induce pubertal changes, various dosing regimens are suggested. For delayed puberty, treatment starts lower than dosages listed here & treatment is shorter in duration (4-6 mo.).	3-6 months	None	Can be used in pre-puberty patients; bone age assessment should be monitored to determine treatment effect on epiphyseal center. Not for late-onset hypogonadism treatment	Long-term sustained release up to 6 months, reducing the number of office visits to 2-4/year.	Infection at the implant site along with extrusion of pellets. Less flexible dosage adjustment compared to shorter-acting treatments

Administration Route	Product Name/Mfr.	Dose (mg)	Duration	Black Box Warning	Patient Population	Advantages	Disadvantages
Nasal	Natesto® 5.5 mg per metered pump actuation [a, b] Acerus Pharmaceutical, 2021	Starting dose of 11 mg (1 pump actuation per nostril) 3x/day. No titration required; check serum T levels 1 month after starting treatment. No titration dose.	Three times daily	None	18 and up; not for late-onset hypogonadism	Easy self-administration with no pain on injection and reduced chance of transference. Short-acting and may maintain spermatogenesis.	If physiological levels are not met, discontinue use. Cannot be used with other nasally administered drugs. May cause runny nose, nose bleed, or other cold-like symptoms.
Testosterone Cypionate							
Intramuscular	Depo®-Testosterone 100 mg/mL(10 mL vial) & 200 mg/mL (1 and 10 mL vials)[a, c] Pharmacia/ Upjohn, 2020	50–400 mg (0.5-4 mL) administered by deep gluteal injection every two to four weeks based on patient response.	2-4 weeks	None	12 and up, not for late-onset hypogonadism	Can be self-administered, flexible dosing. Symptom improvement within 2 days of dosing.	Can have large peak and trough swings prior to next injection causing symptoms due to supra-physiological T levels. Increased risk of polycythemia. Pain at injection site. If not self-injecting, requires many office visits.
Testosterone Enanthate							
Subcutaneous	Xyosted® 50 mg/0.5mL, 75 mg/0.5mL, & 100 mg/0.5mL auto-injector [a] Antares Pharma, 2021	Starting dose of 75 mg subcutaneously administered in the abdomen once weekly. Adjust dose based on serum T trough levels at 7 days after most recent injection after 6 weeks of treatment and periodically thereafter.	1 week	Yes - increased blood pressure can increase MACE risk, including non-fatal myocardial infarction, non-fatal stroke, and cardiovascular death.	18 and up; not for late-onset hypogonadism not associated with structural or genetic etiologies.	Can be self-administered with auto-injector, flexible dosing. Symptom improvement within 2 days of dosing.	Can have large peak/trough swings just prior to next injection causing symptoms due to supra-physiological T levels. There is an increased risk of polycythemia. Pain at injection site. If not self-injecting, requires many office visits.

Administration Route	Product Name/Mfr.	Dose (mg)	Duration	Black Box Warning	Patient Population	Advantages	Disadvantages
Testosterone Undecanoate							
Oral	Jatenzo® 158 mg, 198 mg & 237 mg capsules [a, d] Clarus Therapeutics, 2021	Starting dose of 237 mg 1x in morning and 1x in evening, taken with food. Dose adjustment from 158 mg to 396 mg twice daily based on serum T levels taken 6 hr after morning dose on at least Day 7 after starting treatment or following dose adjustment.	Twice daily	Yes–increased blood pressure can increase MACE risk (e.g., non-fatal myocardial infarction, non-fatal stroke, cardiovascular death.	18 and up; not for late-onset hypogonadism not associated with structural or genetic etiologies.	Easy and convenient self-administration. Best for patients requiring low levels of T and those that cannot tolerate other dosage forms.	Best when taken with fatty meal due to low bioavailability w/ high inter- and intra-variability. Normal T levels sustained for 3-5 hr per day.
Intramuscular	Aveed® 750 mg/ 3 mL ampule [a] Endo Pharmaceuticals, 2021	Initial dose of 3 mL (750mg) followed by a 3mL (750 mg) dose after 4 weeks, then every 10 weeks as a slow deep gluteal injection. No titration required.	10 weeks (A loading dosing is required 4 weeks after the initial dose)	Yes–potential POME reaction and/or anaphylaxis requires REMS program	18 and up; not for late-onset hypogonadism	Physiological levels of T are maintained for 10 weeks with a continuous steady state profile. Reduced peaks/troughs compared to shorter-acting treatments. No implant extrusion. Approximately 5 injections/year.	Injection site reactions/pain at injection site. Requires office visit for administration with 30-min waiting period after injection to observe for possible POME symptoms. Inability to withdraw if adverse event occurs.

[a] "An update on the available and emerging pharmacotherapy for adults with testosterone deficiency available in the USA," by E. Kresch, M. Patel, T. F. N. Lima, and R. Ramasamy, 2021, *Expert Opinion on Pharmacotherapy*, *22*(13), 1761–1771 (https://doi.org/10.1080/14656566.2021.1918101).

[b] "Natesto effects on reproductive hormones and semen parameters: Results from an ongoing single-center, investigator-initiated Phase IV clinical trial," by T. Masterson, M. Molina, E. Ibrahim, and R. Ramasamy, 2018, *European Urology Focus*, *4*(3), 333–335 (https://doi.org/10.1016/j.euf.2018.08.009).

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CHAPTER 4

EVALUATION, MONITORING, & OUTCOMES

Treatment Evaluation & Monitoring

Patients should be evaluated at least 3 months after treatment initiation or based on TRT option recommendations, and then annually to assess treatment response and determine if any adverse events are occurring. Additionally at this time, men should have PSA values rechecked based on current guidelines and recommendation based on age and race. TRT should restore testosterone levels to the mid-normal range of healthy men. For testosterone esters with cypionate and enanthate, testosterone concentrations should generally be measured at the half-way point between injections. The next dose or dosing frequency should be adjusted if testosterone is greater than 700 ng/dL or less than 350 ng/dL (Bhasin et al., 2006). If testosterone levels are elevated above physiologic levels, patients can experience aggressive and violent behavior, mania, and at the extreme suicidal ideation and suicide. Supraphysiological levels can also lead to increased acne and increased risk of thrombosis if Hct > 54% (Ruige et al., 2013).

Hematocrit levels should be evaluated at baseline, 3–6 months after therapy start, after 12 months from therapy start, and then annually. TRT should be stopped if hematocrit is 54% or greater; therapy can be re-started at a reduced dose once values return to a safe level and the patient has been evaluated for sleep apnea and hypoxia (Bhasin et al., 2018; Bhasin et al., 2006). After 1 to 2 years of TRT, men with hypogonadism and osteoporosis or low trauma fracture should have their bone mineral density evaluated (Bhasin et al., 2006).

At each visit, patients should be evaluated for signs and symptoms of adverse events specifically related to the form of TRT the patient is receiving. Specific to short-acting injectable

formulations, mood and libido fluctuations should be evaluated as well as hematocrit, especially in older patients, to determine if there is excessive erythrocytosis (Bhasin et al., 2006).

Treatment Outcomes

Benefits of TRT

Once a clinical diagnosis of low-T has been given, therapeutic intervention begins. The benefits to treatment with exogenous testosterone are numerous and there is a clear increase in the quality of life in patients receiving treatment. After treatment begins, men report increases in muscle mass and strength, improvement in mood and energy levels, and increases in sexual interest, awareness, and arousal (Vermeulen, 2001); increases in bone mineral density also have been reported (Behre et al., 1997).

TRT should improve quality of life by reversing or preventing the symptoms and long-term effects of hypogonadism by creating such benefits as: induction or completion of secondary sexual development, and improved libido, sex drive, and sexual function as well as improved mood and well-being, support of muscle mass and lean muscle gains, restoration or maintenance of masculine characteristics (facial and body hair), maintenance of bone strength (to prevent osteoporosis) and maintenance of red blood cell production (to prevent anemia). TRT can improve the sex drive and mood in 3–6 weeks; however, effects on muscle and bone can take 6–12 months of treatment before benefits are seen (Bassil et al., 2009; Jayasena et al., 2022; Saad et al., 2011). These benefits have aided prescription sales in the United States, which have increased more than 500% since 1993 (Bassil et al., 2009).Table 5 presents a synopsis of the benefits of treatment.

Table 5

Benefits of Testosterone Replacement Therapy

Benefit	References
• Improvement to mood and sense of well being • Better metabolic control • Improved sexual function • Improvement to concentration • Improved sleep quality • Mental health and physical fitness • Increased libido and reduced ED symptoms • Increased lean muscle and strength • Improved bone mineral density • Decrease in fat mass • Positive effect on glycaemia and lipid profiles • Increased energy	(Bassil et al., 2009; Dudek et al., 2017; Jayasena et al., 2022; Saad et al., 2011)

Risks of TRT

Although there are clearly numerous benefits to TRT, there has been a rise in reports of risks associated with exogenous testosterone. The potential risks associated with TRT can vary and are often dependent on the type of treatment received. Risks can be as serious as increases in adverse cardiac events (Basaria, 2014; Bhasin & Basaria, 2011; Ramasamy et al., 2014) to as innocuous as skin irritation (Bhasin & Basaria, 2011; Rhoden & Morgentaler, 2004).

The risks involved are strongly correlated to comorbidities and the type of clinical intervention, which should be strongly considered when deciding on a treatment method. Testosterone replacement therapy is believed to increase the incidence of severe obstructive

sleep apnea, pre-existing erythrocytosis, prostate cancer growth, and adverse cardiac events such as congestive heart failure (Basaria, 2014; Bhasin, 2006; Bhasin & Basaria, 2011; Rhoden & Morgentaler, 2004; Vermeulen, 2001). Patients receiving TRT should be monitored closely and a PSA test to monitor for the potential of prostate cancer should be done prior to start of treatment and with increased frequency during treatment (Bhasin & Basaria, 2011). While the increase in cardiac events associated with TRT is not fully understood, it must be noted that there have been reports of increases in the incidence of stroke and myocardial infarction. Patients' cardiac function should be closely monitored and considered prior to the initiation of TRT (Bhasin & Basaria, 2011). Table 6 presents the risks associated with treatment.

Table 6

Risks of Testosterone Replacement Therapy

Treatment Risks	Citations
• Erythrocytosis • Acne and oily skin • Gynecomastia and breast tenderness • Leg edema • Heart failure* • Growth of metastatic prostate cancer* • Detection of subclinical prostate cancer* • Infertility • Worsening sleep apnea • Growth of breast cancer* • Male pattern baldness • Skin irritation** • Infection** • Renal insufficiencies • Lower-urinary-tract- symptoms • Polycythemia • Increased incidence myocardial infarctions • Increased strokes	(Basaria, 2013, 2014; Basaria & Dobs, 2001; Bhasin & Basaria, 2011; McGill et al., 2012; Ramasamy et al., 2014; Rhoden & Morgentaler, 2004; Vermeulen, 2001)

* Medical history and risk should be evaluated prior to TRT start.
** Dependent on route of administration and formulation type.

Furthermore, patient education is very important in mitigating risks and communicating side effects. Patients should be educated on potential side effects and management to increase compliance. Potential side effects are acne, headache, irritability, aggression, mood swings, depression, weight gain, edema, prolonged painful or frequent erections, gynecomastia, and irritability (Bhasin et al., 2018; Jayasena et al., 2022). When patients do not understand the benefits, risks, side effects, or dosage regimen of medications, rates of treatment discontinuation increase. In patients being treated with dermal products treatment continuation rates after 3 months were 52% and rates of 31% were reported for those on short-acting IM injectable TRT. After 1 year, only 18% of topical TRT users and 5% of short-acting injectable TRT users remained on therapy. These low retention rates reinforce the importance of patient education (Donatucci et al., 2014).

Like the correlation with cardiovascular risk, the connection of TRT with greater bone strength and density is not yet understood. While it is assumed that fracture rates will decrease in men being treated with TRT, patients should work with their doctors to determine if osteoporosis-specific medications should be initiated in older men with osteoporosis and an increased risk of fracture in addition to TRT, as hypogonadism can reduce bone mineral density in this population. Younger men not requiring osteoporosis treatment should wait until TRT bone mineral density improvements stabilize to determine if osteoporosis-specific medications are required (Jayasena et al., 2022).

Testosterone replacement therapy has historically been contraindicated for individuals diagnosed with or suspected to have prostate cancer, the indicators of which include elevated PSA, induration, and prostate nodules; therefore, those with such indications should be further evaluated prior to TRT (Bhasin & Basaria, 2011). Men with a PSA value of > 4 ng/mL should

not start TRT nor should men at increased risk for prostate cancer (e.g., immediate family member with prostate cancer, African Americans) with a PSA > 3 ng/mL, without further evaluation of urological health; those with elevated Hct or who have had a major cardiac event in the last 6 months should also not start TRT. Men with prostate cancer should work with their team of urologists/urologic oncologists and endocrinologists to determine if TRT is an option. The relationship between TRT and the development of prostate cancer has long been debated. Recent literature has shown no significant increase in prostate cancer diagnosis in men on TRT (Bell, et al., 2018; Brock et al., 2016; Mulhall et al., 2018; Snyder et al., 2016). However, the FDA still warns of the potential risk of prostate cancer with TRT. Men with in situ prostate cancer should discuss TRT options with their team of specialists as the benefit-to-risk ratio is not fully understood. Men who have undergone radiation therapy or radical prostatectomy should not be ruled out for TRT. Data for these groups are limited, and patients should speak with their team of specialists to determine if TRT is appropriate. PSA levels should be routinely monitored in prostate cancer patients on TRT (Mulhall et al., 2018).

Prostate cancer is the number one non-dermatological cancer and the second leading cause of cancer death in men in North America and Europe (Siegel et al., 2020). Men that have not been diagnosed with prostate cancer should be able to receive TRT even as they continue to age as no correlation has been found linking TRT to an increased rate of prostate cancer (Lenfant et al., 2020). All men, regardless of being prescribed TRT, should follow recommended guidelines and speak with their doctors regarding prostate cancer screening (Jayasena et al., 2022).

Many approved TRT options contain a black box warning regarding cardiovascular events, which have been a historical topic of scrutiny (see Table 4). Based on Jayasena et al.'s

(2022) review of cardiovascular and cerebrovascular events, there is still a lack of confirmed/consistent correlation with TRT, either positive or negative. Patients, especially those with increased risk for cardiovascular events, should be educated that cardiovascular risks and TRT are currently being investigated (Jayasena et al.).

Low-T levels are associated with increased major cardiac events (e.g., stroke, myocardial infarction, cardiovascular-related mortality); patients should be made aware of this increased risk factor (Kloner et al., 2016; Mulhall et al., 2018). While low-T may increase the risk of MACE, there is still uncertainty and controversy regarding whether TRT increases or decreases such incidents. Patients receiving TRT should report signs of cardiovascular-related issues (e.g., chest pain). TRT should not be prescribed to men who have had a cardiovascular event in the 3-6 months prior to treatment initiation. After the waiting period, if TRT initiation has been decided upon, cardiovascular monitoring should be strictly adhered to (Mulhall et al., 2018).

CHAPTER 5

DISCUSSION

During the development of this literature review, it became apparent that the treatment guidelines for hypogonadism are ever-changing. Most notably, the stance taken by the Endocrine Society and the AUA to treat those with late-onset hypogonadism have evolved over time. It will be up to pharmaceutical companies to perform clinical trials to acquire FDA-approval that establishes LOH as an independent, treatable condition that warrants the use of TRT, where safe and appropriate. Given that TRTs currently are indicated specifically for primary and secondary hypogonadism only but off-label use is permitted to aid in the treatment of many different conditions (e.g., HIV+) to aid in such things as maintaining or increasing muscle mass and lean body mass, this is a reasonable and appropriate recommendation. For example, there are research efforts underway looking into common conditions and symptoms that TRT is being used for as a "quick-fix" to alleviate issues caused by comorbidities (e.g., obesity), in part due to how many symptoms of hypogonadism are non-specific.

The use of TRTs when true hypogonadism is not present can cause side effects from mild to severe as well as increase the likelihood of the development of new problematic conditions or the intensifying of other unwanted conditions, such as gynecomastia. TRT use should be carefully considered by physicians before the topic is proposed with patients and the benefits, risks, and potential side effects must be clearly indicated with the individual patient prior to embarking on a course of treatment.

The use of TRTs has not just increased over the years, the methods of delivery have evolved as well. One significant finding of this research is the lack of a long-acting injectable

that does not pose the risk of POME that has been found to be associated with Aveed's oil formulation. In addition, future research is needed to explore the potential for new testosterone formulations. Another area that merits further examination is that of establishing a basis for the use of TRT in patients with an LOH diagnosis.

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