

## Testosterone Therapy With a Man With Equivocal Testosterone Levels

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Clarifying what are normal testosterone (T) levels is not an easy task. Normal levels should always be determined using laboratory-specific reference range. Data derived from the literature are conflicting since, different *Scientific Societies* have proposed several different thresholds for normality, according to a consensus of experts or by analysis of normal distribution of T levels across different age bands, based on harmonized epidemiological studies. For instance, the Endocrine Society proposed in healthy, non-obese, young men, as a limit of low total T, 264 ng/dL (9.2 nmol/L).<sup>1</sup> However, a recently published Australian randomized controlled trial (RCT) – enrolling more than 1,000 obese subjects with baseline total T < 14 nmol/L and prediabetes or type 2 diabetes mellitus – shows impressive, significant results on glucose tolerance in the treated arm with intramuscular injection of 1,000 mg T undecanoate every three months for 2 years.<sup>2</sup> Interestingly, when enrolled subjects were divided according to baseline T levels below or above 11 nmol/L, no differences were found in the primary outcome (glucose tolerance) between these two categories. Loss of sexual drive is considered the most genuine symptom of late onset hypogonadism, because it is less affected by the presence of age-associated comorbidities.<sup>3</sup> In a previous meta-analysis of the placebo controlled RCTs, outcomes on sexual desire were similar in the placebo and TRT arms either when only those studies enrolling hypogonadal subjects or those enrolling a mixed eugonadal/hypogonadal population were considered.<sup>4</sup>

The aforementioned findings suggest that TRT could indeed be effective in improving sexual desire also in subjects with borderline or apparently normal T levels. However, we must clarify that there are several congenital or acquired conditions that are associated with features of androgen deficiency despite normal or even increased T levels (see Table 1; reference 5). The latter conditions are characterized by a total or partial lack of the entire spectrum of androgen actions as a consequence of the inactivation of the androgen receptor (AR, eg, Morris and Kennedy syndromes) or due to an impaired transformation of T in its

bioactive metabolites, such as estrogens or dihydrotestosterone (DHT). The latter can be due to rare congenital conditions (aromatase or type 2 5 $\alpha$ -reductase mutations) or, more often, because subjects were taking medications that elicit a similar effect (aromatase or 5 $\alpha$ -reductase inhibitors, 5ARI;<sup>5</sup>). Non-steroidal medications that block the activity of the androgen or of the estrogen receptor might also result in increased T levels, compromising the DHT- or estrogen-dependent functions of T, however.<sup>5</sup> In all the aforementioned conditions, there is an increase in luteinizing hormone levels because the negative feedback exerted by the sex steroids on the hypothalamus and pituitary gland is impaired or interrupted. As a consequence, T rises but its biological activity is partially impaired. An impaired T-derived estrogen formation or an impaired estrogen action is associated, in males, with altered bone metabolism and osteoporosis and, most probably, with decreased sexual desire.<sup>3,5</sup> An impaired DHT formation is associated with erectile dysfunction and decreased libido,<sup>6</sup> along with gynecomastia, decreased prostate size and PSA levels. It is important to note that besides classical 5ARIs, such as finasteride and dutasteride, other medications could impair DHT formation. In fact, one of the most widely used phytotherapeutic preparations for the treatment of lower urinary tract symptoms are based on *Serenoa Repens*, a weak blocker of 5 $\alpha$ -reductase activity. The herbal preparations based on this compound are not devoid of sexual side effects, such as loss of libido and gynecomastia.<sup>7</sup>

A common condition, in the general male population, associated with symptoms of androgen deficiency along with normal T levels, is an increased hepatic production of sex hormone binding globulin (SHBG), a T binding protein which shows a 3-fold higher affinity for T than for estrogens. According to the free hormone hypothesis, only the fraction of T not bound to SHBG (free T) can exert biological effects. SHBG activity can be increased by a genetic polymorphism of the SHBG gene.<sup>8</sup> More often, increased SHBG levels might be concomitant to physiological and pathological conditions as listed in Table 1. Increased levels of SHBG are associated with genuine symptoms and signs of T deficiency, including sexual symptoms and a decreased PSA.<sup>3,5</sup> Preclinical studies in a transgenic mouse model overexpressing human SHBG confirmed this clinical observation.<sup>9</sup> In addition, an epidemiological study, performed in the European general population, confirmed that increased SHBG level (and a consequent decrease of free T) is associated with typical hypogonadal symptoms, even in the presence of normal T levels.<sup>10</sup> Furthermore, in a longitudinal extension of the same study, it has

Received January 30, 2022. Accepted March 13, 2022.

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<https://doi.org/10.1016/j.jsxm.2022.03.601>

**Table 1.** Conditions associated with androgen deficiency in the presence of normal testosterone levels

Congenital	
<i>Impaired sex steroid receptor activity</i>	
	AR inactivating mutations (Morris Syndrome)
	Kennedy Syndrome
	ER $\alpha$ inactivating mutations
<i>Increased SHBG activity</i>	
	genetic variants in the SHBG locus
<i>Impaired T conversion to bioactive metabolites</i>	
	Type 2 5 $\alpha$ reductase mutations
	Aromatase mutations
Acquired	
<i>Impaired sex steroid receptor activity</i>	
	Non-steroidal AR antagonists
	ER antagonists
<i>Increased SHBG production</i>	
	Aging
	Antiepileptic medications
	Hyperthyroidism
	Estrogens
	Hepatic disorders
<i>Impaired T conversion to bioactive metabolites</i>	
	Type 1 and type 2 5 $\alpha$ reductase inhibitors
	Aromatase inhibitors

AR = androgen receptor; ER = estrogen receptor; SHBG = sex hormone binding globulin.

been demonstrated that reduced free T, but not reduced total T, is an essential prerequisite for identifying an incident symptomatic secondary hypogonadism.<sup>11</sup>

In conclusion, what to do in subjects showing the signs and symptoms suggestive of T deficiency, but with normal levels of total T? Before answering this important question, it should be recognized that sexual problems (erectile dysfunction, ED, and loss of libido) are, on one hand, the symptoms most closely related to T deficiency, but, on the other hand, they suffer from a very low specificity, as they have multiple possible determinants besides androgen deficiency. Nonetheless, in potentially symptomatic subjects with normal T levels, the first step is to investigate whether or not they are taking medications that might impair the biological activity of T, such as those interfering with T binding to the AR or with the formation and action of DHT or estrogen. Several of these medications are often used, in particular, in the aging male. In addition, SHBG levels should be systematically measured in order to obtain a calculation of the free

amount of T (cFT) that is more indicative than total T itself of the real androgenization of the patient. If cFT results as being normal, along with a negative pharmacological medical history, it is possible to consider doing an investigation into analytes that are downstream from the action of the AR, such as hematocrit and PSA. PSA is an androgen-dependent prostatic protein, with 3 AR responsive elements in its promoter.<sup>3</sup> Its androgen-dependency is mostly evident in the hypogonadal range.<sup>3,12</sup> Hence, low levels of PSA, along with decreased prostate volume, could suggest a functional androgen deficiency. Considering that PSA levels increase as a factor of age, different thresholds should be used for the suspicion of androgen deficiency according to different age bands. In a population of 3,156 subjects with ED, among the youngest individuals, a PSA level below 0.56 ng/mL was suggestive of an androgen deficiency with a specificity and sensitivity of more than 60%.<sup>12</sup> However, PSA levels do not only reflect the androgen status but they can also be influenced by common prostatic disturbances, such as inflammation, enlargement or even cancer. Hence, in older individuals, where these conditions are present more often, even a higher PSA threshold (ie, 0.97 ng/mL) suffers from a lower sensitivity and specificity for an androgen deficient status.<sup>12</sup> Hematocrit is another easy-to-obtain indicator of T bioactivity.<sup>3</sup> In fact, T increases erythropoiesis and alters iron homeostasis via elevation of erythropoietin and suppression of hepcidin level.<sup>3</sup> The final result is a T-dependent increase in hematocrit. Accordingly, polycythemia is the most frequently observed side effect of TRT in RCTs.<sup>3</sup> However, even the hematocrit is influenced by several other determinants that strongly limit its utility in the suspicion of an androgen deficiency. Hence, thus far, we do not have specific indicators of the action of androgens on their receptors.

Genetic studies on the AR could offer important insight into the most severe forms, as in complete AR resistance (ie, Morris Syndrome). However, in the mildest forms of resistance, such as those characterizing an expanded CAG repeat in exon 3 of AR, the hypothalamus-pituitary-testis axis resets itself because of a variation in the negative feedback, compensating for the diminished bioactivity of AR with a resulting minimal or null effect on phenotype.<sup>13</sup> Hence, studying CAG repeat length is not useful in understanding the biology of androgen deficiency in the normal population, although it can be useful for pharmacogenetic purposes.

It should be recognized that annually T decline is quite variable depending on a combination of genetic and epigenetic factors.<sup>14</sup> Quite recently, the concept of “*Testosterone Annual Decrease Velocity*” has been proposed to be responsible for the development of hypogonadal related symptoms, even in the presence of normal T levels based on the degree of the intra individual T annual variation.<sup>15</sup> However, it should be clarified that no sufficient data are available to support the latter hypothesis.

Finally, limited evidence has shown that subclinical hypogonadism, a condition characterized by increased luteinizing hormone and normal T levels, can be associated with poor health

and increased cardiovascular mortality and morbidity.<sup>16</sup> Whether or not TRT can improve subclinical hypogonadism outcomes is unknown at present time.

In conclusion, due to limited evidence related to TRT outcomes based on cFT levels, current guidelines mainly based their recommendations on total T levels.<sup>14,17,18</sup> Concerning TRT in symptomatic subjects with normal T levels, our opinion is to consider for treatment only those with a low cFT, which in our experience corresponds to a value lower than 225 pmol/L.<sup>19</sup> Having low PSA and/or low hematocrit levels could support possible treatment.<sup>3,5</sup> For all the other cases, mainly represented by overweight or obese men, changes in lifestyle, including physical exercise and dieting could improve symptomatology besides favoring a rise in T.<sup>20</sup> In particular, available data show each five kilogram of weight reduction, whatever obtained result in one nmol/L of T level increment.<sup>21</sup> This should be offered also to all the symptomatic subjects with borderline low total T, because it can overcome the underlying condition.<sup>20</sup> A complementary option is to also offer a PDE5 inhibitor, which not only can improve the sexual dysfunction but can also increase endogenous T.<sup>22</sup>

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**Conflict of Interest:** The authors report no conflicts of interest.

**Funding:** None.

## STATEMENT OF AUTHORSHIP

Giovanni Corona: Conceptualization, Methodology, Software, Validation; Mario Maggi: Formal Analysis, Investigation, N/A; Giovanni Corona and Mario Maggi: Resources, Data Curation, Writing – Original Draft, Writing – Review & Editing, Visualization, Supervision, Project Administration; N/A; Funding Acquisition

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