

# A Brief Review: Testosterone and Resistance Exercise in Men

Chad C. Loebel and William J. Kraemer

Laboratory for Sports Medicine, Kinesiology Dept., The Pennsylvania State University, University Park, Pennsylvania 16802.

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## Reference Data

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## ABSTRACT

Testosterone is a steroid hormone that is secreted in men from the testes in a circadian fashion. Secretion of testosterone from the testes is indirectly controlled by the hypothalamus. In order for secretion to occur from the testes, the hypothalamus must first secrete leutinizing hormone-releasing hormone. Previous research has consistently shown increases in serum testosterone concentration following acute resistance exercise. Testosterone is affected by a combination of factors including the amount of muscle tissue mass stimulated, volume of exercise performed, and intensity of exercise. Testosterone plays important regulatory roles in muscle protein metabolism and influences neuromuscular trainability. There is a circadian rhythm of testosterone, but to date no data exist as to the effects of resistance exercise on the diurnal cycle of testosterone. This area of study should be investigated further in order to gain greater understanding of how resistance exercise affects testosterone responses over the course of a entire day.

**Key Words:** androgens, strength, muscle, neuromuscular, anabolic hormones

## Introduction

Testosterone, a steroid hormone, is secreted in men from the testes in a circadian fashion. In general, both serum (11, 22, 60, 76) and salivary (4, 58) testosterone achieve maximal concentrations in the morning and minimal concentrations in the evening. Because of this relationship between serum and salivary testosterone, the latter is also commonly used as a marker of gonadal function in men. The circadian rhythm of testosterone has been the focus of considerable research dating back to the mid-1960s. Research supports the evidence of a circadian rhythm of testosterone in humans, but these patterns are highly individual and variable in various study populations (89).

Secretion of testosterone from the testes is indirectly controlled by the hypothalamus. In order for the testes to secrete testosterone, the hypothalamus must first secrete leutinizing hormone-releasing hormone. It is believed that this hormone is secreted from the hypothalamus in a circadian manner (93). This secretion pattern will cause a similar response pattern of leutinizing hormone which has also been shown to have a circadian rhythm (97). The testes are then activated by leutinizing hormone to secrete testosterone.

Previous research has consistently shown increases in serum testosterone concentration following acute resistance exercise (26, 43). With the exception of research by Jensen et al. (49) and Chandler et al. (15), who studied continual serum testosterone responses 6 and 8 hours postexercise, respectively, most research has illustrated frequent sampling ranging from 0 to 120 minutes postexercise. However, many studies have examined the effects of resistance exercise on the immediate postexercise concentrations of serum testosterone. The effects have included both physiological and performance factors (48). As mentioned, there is a circadian rhythm of testosterone, but to date no data have been published as to the effects of resistance exercise on the diurnal cycle of testosterone. This would be a fertile area of study for future investigations.

Interestingly, studies have shown that circadian rhythms occur in anaerobic and aerobic power tests (46, 47). Athletes may be affected by altered testosterone concentrations (41), and this hormone may be important for the trainability and/or performance ability of athletes (75). Possible alterations in testosterone's circadian rhythm due to resistance exercise may provide insight into performance variables and adaptational mechanisms.

## Physiology of Testosterone

### *Testosterone Synthesis and Secretion*

Testosterone is a steroid hormone produced almost entirely by Leydig cells which are found in the interstitial tissue in the testes. Some minor amounts are also secreted from the prostate, skin, and liver. Normal serum

values typically range from 14.0 to 28.0 nmol · L<sup>-1</sup> or 4.0 to 8.0 ng · ml<sup>-1</sup> in men (106). In men under the age of 30 years, concentrations typically are above 18.0 nmol · L<sup>-1</sup>; as men age, testosterone concentrations decrease and by the sixth decade of life can be measured below 12 nmol · L<sup>-1</sup>. Thus, aging has dramatic effects on resting concentrations of testosterone and can also affect the ability of older men to increase testosterone following acute resistance exercise.

Cholesterol, testosterone's precursor steroid, can either be synthesized *de novo* or derived from endocytosis of low-density lipoproteins (25). Approximately half of the testosterone produced in the testes is derived from *de novo* cholesterol synthesis. The key stage in the synthesis of testosterone is the conversion of cholesterol to pregnenolone. This step is rate limiting (13) and involves the side-chain cleavage of cholesterol by way of hydroxylation. Cleavage of cholesterol takes place in the mitochondria where the enzymes required for side-chain cleavage are present. Leutinizing hormone serves as a regulatory control of this cleavage process (25) by promoting the synthesis of a protein that carries cholesterol to the site of cleavage in the mitochondria.

The most active form of testosterone is in the free, or unbound, form. This accounts for approximately 2% of all testosterone; 38% is bound to albumin while the remaining 60% is bound to sex hormone-binding globulin (98). The 40% of testosterone that is not bound to sex hormone-binding globulin is available for metabolism. Only the unbound fraction of the steroid hormone in the plasma is freely exchangeable with the extravascular and intracellular compartments (13).

Such findings have led to the development of the "free hormone" hypothesis as the primary way testosterone interacts with cells. Interestingly, the bound fraction of testosterone appears to ultimately control the amount of hormone that goes into a free or unbound state. Thus, while it is the free hormone that interacts with the cell's nuclear receptor, it is the bound fraction that dictates the amount of hormone available. Testosterone receptors must be up-regulated in order to interact with the free hormone. If a receptor is down-regulated, no interaction will occur with the free hormone. This mechanism of up and down regulation allows individual target cells (e.g., muscle) to interact differentially with the free hormone.

The impact of such a mechanism explains the differential response of Type I and Type II fibers to resistance training (28). Type I fibers typically fight large size increases by down-regulating testosterone receptors in response to anabolic exercise stimuli such as resistance training. Conversely, Type I fibers up-regulate in response to sole oxidative endurance training exercise stress to help maintain protein levels in the face of increased degradation due to the stimulus to decrease Type I fiber size for improved oxygen kinetics (28).

### *Role in Human Development*

Testosterone plays vital roles in the development of the human body from conception on. Seventy days into fetal life, testes enlarge and undergo a short period of activity. During this time period, testosterone is synthesized from a number of precursors and can be measured in fetal plasma (77). The testes are active throughout the first year of life (31) and then testosterone concentrations decline until puberty. Concentrations of testosterone rise again at the onset of puberty, with increases becoming evident during sleep. These increases are associated with secretory bursts of leutinizing hormone (9).

Testosterone is a sex related hormone responsible for many androgenic/anabolic properties (54), and developmental phases throughout life rely upon the proper timing of testosterone release (38). In the skin and reproductive tract, testosterone is responsible for hair growth and production of secretory proteins (64). In the kidneys, androgens will cause nephron tissues to hypertrophy and will cause an increased erythropoietin synthesis (94). After testosterone is converted to estrogen (96), brain development is controlled by testosterone via an estrogen receptor complex.

All testosterone associated developmental functions are performed by the same mechanism at the cellular level. Although the tissues and organs affected by testosterone are diverse, a hormone-receptor complex is necessary for any testosterone mediated effect to occur. The multitude of tissues that interact with testosterone allow for a greater spectrum of training effects when endogenous increases are seen with exercise. In addition, it is obvious that the use of synthetic testosterone with anabolic drug use affect more than the one target tissue.

### *Role in Muscular Development*

Testosterone is a potent stimulator of muscle protein synthesis (8, 29, 30). As previously stated, a hormone receptor complex must be present for the action of testosterone to occur. These complexes may occur in the cytosol and then translocate to the nucleus (65, 69), or they may occur directly in the nucleus itself (84, 88). Regardless of the location, activation of the receptor-hormone complex will increase mRNA and DNA synthesis. This increase in action will lead to increased protein accretion via increased intramuscular amino acid uptake (3).

Testosterone also possesses anticatabolic properties within skeletal muscle. Inhibition of muscle glycogen breakdown (5, 33) and displacement of glucocorticoid via attachment to its receptor (66) are two powerful mechanisms of skeletal muscle protein retention. Cortisol's signal is typically related to the loss of glycogen stores in the muscle and the need for glucose. Oftentimes, cortisol increases may be related to other stress factors beyond carbohydrate metabolism and

may affect protein breakdown (19, 59, 95). The response of testosterone to offset this effect on protein metabolism can be vital for maintaining muscle size and function.

### Circadian Secretion of Testosterone

Circadian rhythms of serum testosterone in men have previously been observed. Studies that show a circadian rhythm (2, 6, 10, 11, 16, 20, 22, 23, 27, 34, 40, 50, 60, 61, 70, 72, 73, 76, 80, 85–87, 89, 93, 99, 105) generally report the highest concentrations in the morning and lowest concentrations in the evening. Due to testosterone's highly individual and variable secretion pattern (89), no specific timeline can be drawn for testosterone secretion. Only general patterns of testosterone's diurnal rhythm can be conceptualized and discussed.

Reports that do not illustrate a circadian rhythm for testosterone (1, 7, 52, 53) have had flaws in their timeline of sampling. Frequent sampling is necessary for proper delineation of circadian rhythms (80, 89). Studies that have not shown a circadian rhythm employed large intervals between sampling times, ranging from 3 to 12 hours. These large breaks in sampling times may be a cause of error. Since the half-life of testosterone is smaller than the nonsampled time interval, rapid variations of diurnal rhythm may not appear (61).

As previously mentioned, testosterone secretion is indirectly controlled by the hypothalamus. Secretion of leutinizing hormone-releasing hormone from the hypothalamus is the primary stimulator for leutinizing hormone and follicle-stimulating hormone release from the pituitary gland (82). This central nervous system peptide is controlled by the hypothalamic pulse generator and is secreted in a pulsatile manner (17) with the number of secreted pulses ranging from 8 to 14 per 24-hour period in normal men (67).

Upon stimulation from leutinizing hormone releasing hormone, the pituitary gland will secrete both leutinizing hormone and follicle-stimulating hormone. Both hormones are glycoproteins secreted by the same basophilic cells in the anterior pituitary. Both are stored in granules that are released through exocytosis with stimulation from leutinizing hormone-releasing hormone.

Rhythmicity of gonadotropin secretion does exist for leutinizing hormone and follicle-stimulating hormone. Past research has shown daily variations, consistent with testosterone variations, of the two gonadotropins with highest levels observed in the morning and lowest levels in the evening (72). Leutinizing hormone is released in episodic bursts as well as tonically in men (71). Although the two hormones are harmonious in their cross-correlated levels (89) and temporal coupling (97), follicle-stimulating hormone is secreted in smaller amplitude pulses due to its longer biological half-life (81).

Leydig cells are stimulated primarily by leutinizing hormone with a slight stimulus from follicle-stimulating hormone to cause testosterone secretion from the testes. A temporal coupling exists between leutinizing hormone and testosterone secretion, with a pulse of testosterone secretion occurring between 10 and 20 (97) to 60 minutes after a pulse of leutinizing hormone (11). Neural innervation of the testes is also responsible in part for testosterone secretion, but the exact extent has not yet been determined (79).

Leutinizing hormone interacts at the Leydig cells with specific high-affinity receptors. Upon receptor binding, a cAMP second messenger system activates Leydig cell protein kinase activity which increases testosterone formation by way of enhancing cholesterol side-chain cleavage (12). Activation of the Leydig cells is dependent on the frequency and amplitude of leutinizing hormone pulsatility (24). The secretory pulses of testosterone range from 8 to 14 per 24-hour period (37), which is approximately the same frequency of leutinizing hormone-releasing hormone secretion from the hypothalamus.

A variety of other factors are also implicated in the presence of a circadian rhythm of testosterone. Negative feedback mechanisms help to counter testosterone's secretion. The hormone itself will act upon the central nervous system to slow the hypothalamic pulse generator, which in turn decreases the frequency of leutinizing hormone pulsatile secretion (92). Also, the pituitary gland receives a direct negative feedback, as elevated plasma testosterone concentration decreases leutinizing hormone sensitivity to LH-releasing hormone stimulation. The rate of testosterone clearance may provide a driving force for rhythm of testosterone secretion by way of feedback mechanisms (68). Finally, testicular blood flow, related to the activity of the sympathetic nervous system and adrenal medulla, also assists in the display of a circadian rhythm of testosterone (23).

### Salivary Testosterone

Saliva provides a convenient, noninvasive means of judging serum testosterone concentration. Previous research has examined the reliability of saliva testosterone to depict gonadal function and possible circadian rhythm of the hormone. Numerous reports (4, 35, 51, 58, 63, 78, 83, 102) have shown a circadian rhythm of salivary testosterone, with levels being significantly higher in the morning than the evening. Values of salivary testosterone typically range from 150 to 500 pmol · L<sup>-1</sup> or 45 to 145 pg · ml<sup>-1</sup> in men (74).

The composition of testosterone in saliva may determine its reliability in assessing serum concentrations and overall function of the testes. Khan-Dawood et al. (51) have shown the makeup of salivary testosterone to be 78% free testosterone while serum free testosterone

was reported to be at 4%. This large component of salivary testosterone is due to the fact that sex hormone-binding globulin is not found in the saliva of men (103). Vittek et al. (100) studied the relationship between salivary and serum free testosterone versus salivary and serum total testosterone. They found statistically significant correlations of  $r = 0.97$  and  $r = 0.70-0.87$  for free and total testosterone, respectively. These results may show that salivary testosterone depicts fluctuations of free testosterone in serum more so than total testosterone.

There is temporal coupling between serum and salivary testosterone. Wang et al. (103) have reported that increases in serum testosterone concentration relate to a concomitant increase in salivary testosterone concentrations within 1 hour. The concentration of salivary testosterone is also independent of saliva flow rate from the salivary glands (78). Given all of these factors, salivary testosterone should provide a useful and reliable means of studying the effect of heavy resistance exercise on the circadian rhythm of testosterone (14, 18).

### Testosterone Response to Resistance Exercise

Previous research has indicated that acute, heavy resistance exercise increases serum testosterone concentration after a threshold amount of work has been performed (36). In addition, this elevation is seen in the recovery period from the resistance exercise workout (56, 57). Resistance exercise has been shown to stimulate muscle strength and hypertrophy (62, 90), which is in part due to increases in testosterone. Postexercise increases may be due in part to the adaptation of steroid synthesis and/or secretory capacities of the Leydig cells (56). Another reason for the increase may be a reduced hepatic clearance of testosterone or an alteration of testicular blood flow (91). Hypertrophy resulting from resistance exercise is primarily due to muscular protein accretion (30).

Differential training variables are important factors to consider when striving to achieve training objectives. Each resistance exercise training session is developed around 5 training variables: choice of exercises, order of exercises, number of sets, rest intervals, and load used (28). Alterations to one or more of these variables may significantly change the exercise-induced endocrine response. For example, Kraemer et al. (57) have studied in depth the response of testosterone to differential heavy resistance exercise protocols. One protocol was a hypertrophy session that employed a 10-repetition maximum (RM, the maximum number of repetitions performed during a set of resistance exercise with a prescribed load) for consecutive sets with different exercises and 1-min rest periods. The other was a strength protocol that employed a 5-RM load with different exercises and 3-min rest periods. Both conventions were shown to increase serum testosterone concentrations

postexercise, but the hypertrophy session produced a greater magnitude of the hormonal response.

Overall, most of the literature does agree that resistance exercise, when performed intensely with enough volume and muscle mass resistance exercise, will significantly increase postexercise testosterone concentrations (15, 26, 32, 36, 42, 43, 49, 55-57, 101, 104). Although the resistance exercise protocols were not similar for these studies, testosterone response to this type of exercise appears to be quite consistent. A few studies (21, 39, 44, 45) have shown unchanged or decreased concentrations after resistance exercise. Mechanisms for this remain speculative and may be due to the protocol used, the time of day, and/or the status of testosterone metabolism at the time of measurement. Kraemer et al. (57) have shown dramatic undulating changes in testosterone responses to a given weight training workout.

### Practical Applications

In order to optimize the role of natural testosterone increases to a resistance exercise workout, strength and conditioning specialists must design a program that provides enough total work (e.g., multiple sets), a high enough intensity (5 to 10 RM), and enough muscle mass stimulated (multiple exercises and large-muscle-group exercises). Understanding the role of natural testosterone in the body can shed light on the factors contributing to neuromuscular adaptations with resistance training.

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