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Testosterone Physiology in Resistance Exercise and Training

The Up-Stream Regulatory Elements

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Abstract

Testosterone is one of the most potent naturally secreted androgenic-anabolic hormones, and its biological effects include promotion of muscle growth. In muscle, testosterone stimulates protein synthesis (anabolic effect) and inhibits protein degradation (anti-catabolic effect); combined, these effects account for the promotion of muscle hypertrophy by testosterone. These

physiological signals from testosterone are modulated through the interaction of testosterone with the intracellular androgen receptor (AR). Testosterone is important for the desired adaptations to resistance exercise and training; in fact, testosterone is considered the major promoter of muscle growth and subsequent increase in muscle strength in response to resistance training in men. The acute endocrine response to a bout of heavy resistance exercise generally includes increased secretion of various catabolic (breakdown-related) and anabolic (growth-related) hormones including testosterone. The response of testosterone and AR to resistance exercise is largely determined by upper regulatory elements including the acute exercise programme variable domains, sex and age. In general, testosterone concentration is elevated directly following heavy resistance exercise in men. Findings on the testosterone response in women are equivocal with both increases and no changes observed in response to a bout of heavy resistance exercise. Age also significantly affects circulating testosterone concentrations. Until puberty, children do not experience an acute increase in testosterone from a bout of resistance exercise; after puberty some acute increases in testosterone from resistance exercise can be found in boys but not in girls. Aging beyond 35–40 years is associated with a 1–3% decline per year in circulating testosterone concentration in men; this decline eventually results in the condition known as andropause. Similarly, aging results in a reduced acute testosterone response to resistance exercise in men. In women, circulating testosterone concentration also gradually declines until menopause, after which a drastic reduction is found. In summary, testosterone is an important modulator of muscle mass in both men and women and acute increases in testosterone can be induced by resistance exercise. In general, the variables within the acute programme variable domains must be selected such that the resistance exercise session contains high volume and metabolic demand in order to induce an acute testosterone response.

This review examines androgen endocrine physiology (i.e. testosterone and the androgen receptor [AR]) and its relationship to resistance exercise and training. Knowledge of the general testosterone physiology is important because it is the foundation for understanding the physiological implications of changes in testosterone and AR concentrations. The first section provides an overview of testosterone production and the signals for testosterone production and release. The next section examines the biological effects of testosterone including transport, signalling and physiological functions with special attention given to the importance of testosterone for normal muscle development and maintenance. Finally, the acute and chronic testosterone and AR responses to resistance exercise and training is discussed with the focus on upper regulatory elements: acute exercise programme variable domains, sex and age.

1. Testosterone Production and Release

1.1 Testosterone Production

Testosterone (17β-hydroxy-4-androstene-3-one) is a 0.288 kD C_{19} steroid hormone produced from cholesterol via a series of conversions catalysed by specific enzymes; this process takes approximately 20–30 minutes from initiation to final product.[1] Several of the intermediates in this process are hormones with their own physiological actions and include progesterone, dihydroepiandrosterone (DHEA) and androstenedione; the former is involved in the female reproductive cycle[2] and the latter two have weak androgenic-anabolic effects.[3]

The primary production site of testosterone is the Leydig cells. These cells are only found in the testes, which largely explain the approximately 10-fold higher circulating testosterone concentrations in men compared with women. Testosterone is also produced in smaller quantities in the ovaries and the zona reticularis of the adrenal cortex.[4] This testosterone formation is mainly spillover from the production of other hormones such as cortisol and aldosterone (in the adrenal glands) that share some precursors with testosterone, and estradiol (in the ovaries) for which testosterone itself is a precursor.[5] These shared precursors help explain how the adrenal gland and the ovaries can produce testosterone despite the absence of Leydig cells in these tissues. This spillover, along with peripheral conversion of androgens, is the primary source of testosterone in females and adolescent boys. The absence of functioning cells dedicated to testosterone production and release prevents large acute increases in circulating testosterone in females and adolescent boys in response to exercise. Although peripheral production (e.g. in muscle tissue) of testosterone occurs,[6] this production does not appear to be affected by resistance exercise in humans.[7]

1.2 Hypothalamic-Pituitary-Gonadal Axis

The signal for gonadal testosterone production and release originates in the hypothalamus. The hypothalamus is innervated by the CNS and thus provides a direct link between the nervous and the endocrine systems.[8] Specialized neurons in the hypothalamus produce and secrete gonadotrophin releasing hormone (GnRH).[8] GnRH travels directly to the anterior pituitary gland via the hypothalamic-hypophyseal portal vein. This allows for a quick delivery of the hormonal signal from the hypothalamus to the pituitary target cells. In the anterior pituitary, GnRH stimulates the production and release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) from the gonadotrophs.[8] LH and FSH then enter the circulation and are transported to the gonads. In the gonads, LH stimulates testosterone production in the Leydig cells of men and the theca cells of women. LH binds to a G-protein-coupled membrane receptor; the signal induced by LH activates cyclic adenosine monophosphate-dependent protein kinases (protein kinase A),[9,10] which stimulates the rate-limiting step in testosterone synthesis.[9] Testosterone is a steroid hormone and thus cannot be stored in the cells that produce it; instead, testosterone is released from the cells following production. In women, testosterone is further processed to estradiol in the granulosa cells adjacent to the theca cells. FSH does not appear to have direct effects on testosterone production in men but is important in stimulation of steroid binding protein production in the liver. In women, FSH stimulates the production of pregnenolone in the granulosa cells and steroid binding protein production in the liver. The signal cascade from FSH is similar to that induced by LH in the theca and Leydig cells; the produced pregnenolone can leave the granulosa cells for the theca cells where it can be further processed to testosterone. Finally, FSH stimulates the synthesis of p450 aromatase, which is responsible for the conversion of testosterone to estradiol in the granulosa cell. This system of signalling events from the hypothalamus to the gonads leading to testosterone (and estradiol) production and secretion is termed the 'hypothalamic-pituitary-gonadal axis'.

1.3 Stimulation and Inhibition of the Hypothalamic-Pituitary-Gonadal Axis

The initiation of the hypothalamic-pituitary-gonadal axis, which ultimately leads to increased testosterone release, is caused either by direct nervous stimulation of the hypothalamus by the CNS or by reduced feedback inhibition on the hypothalamus by testosterone. Testosterone induces negative feedback on (i) the hypothalamus to reduce GnRH release; and (ii) the gonadotrophs in the anterior pituitary to reduce the release of LH and FSH in response to GnRH. The use of GnRH analogues have shown that in the absence of a GnRH signal the gonadotrophs in the anterior pituitary do not independently release LH despite very low circulating testosterone concentrations.[11,12] Since the GnRH analogue prevented an exercise-induced increase in

circulating LH and testosterone, it appears that the signal for increased testosterone release with resistance exercise is controlled at the level of the hypothalamus.

2. The Biological Effects of Testosterone

Testosterone is one of the most potent naturally secreted androgenic-anabolic hormones,[13] and its biological effects include promotion of secondary male-sex characteristics, such as beard and body hair growth, nitrogen retention and muscle growth.[14] In muscle, testosterone stimulates protein synthesis (anabolic effect)[15] and inhibits protein degradation (anti-catabolic effect);[16] combined, these effects account for the promotion of muscle hypertrophy by testosterone. The physiological effects of testosterone are induced by its binding to the intracellular AR, which then translocates to the nucleus where the AR-testosterone complex induces transcription of specific genes.[17] Recently, membrane receptors for testosterone have been proposed to explain the rapid effects of testosterone on the cell.[18] In addition to the anabolic effects, testosterone has anti-catabolic effects that are believed to include an inhibition of cortisol signalling by blocking the glucocorticoid receptor.[19,20] The administration of testosterone to patients receiving long-term glucocorticoid therapy attenuates or even reverses some of the adverse effects from glucocorticoid treatment such as reductions in bone mineral density and muscle mass.[21] Similarly, excess glucocorticoids can interfere with testosterone signalling[22] and suppress testosterone production in the Leydig cells.[23] It is mainly the anabolic effects of testosterone that are of interest to those engaged in resistance exercise; however, the anti-catabolic effects might also be a very important aspect because they help protect muscle protein and aid in recovery. These anabolic effects are also primarily what have led athletes from many different sports to abuse various pharmacological forms of testosterone. Although generally not considered among the primary anabolic hormones in women, testosterone has a potent effect on female muscle tissue.

2.1 Transport of Testosterone in the Circulation

Testosterone is hydrophobic and consequently does not readily dissolve in the blood; instead, almost all testosterone in the circulation is bound to binding proteins that are hydrophilic.[24] The primary binding protein for testosterone is sex hormone-binding globulin (SHBG), which binds approximately 44–60% of total serum testosterone.[25,26] The remaining testosterone is either loosely bound to albumin and other binding proteins or free (i.e. not bound to any binding proteins); however, only about 0.2–2% of total testosterone is in the free form.[26,27] Free testosterone is the most biologically active fraction of testosterone; thus, the biological activity of testosterone is regulated by its interaction with the different binding proteins.[28] The physiological effects of the binding proteins vary. SHBG reduces the movement of testosterone from the blood into other biocompartments; whereas, albumin does not appear to interfere with this movement.[29,30] Furthermore, in contrast to free testosterone, binding proteins cannot move across the cell membrane; as a result, association with the binding protein reduces the likelihood for testosterone interaction with the intra-cellular nuclear AR. Binding to SHBG effectively prevents the biological actions of testosterone; whereas, binding to albumin appears to still allow for a large bioavailability of testosterone.[31] In addition to facilitating the transport of the hydrophobic testosterone in the watery environment of the blood, binding proteins reduce the clearance of testosterone from the blood.[29] Testosterone cannot be stored in the cells that produce it, which is in contrast to most peptide hormones, so the association with binding proteins can act as storage in the circulation. The bound testosterone can then be released to become free testosterone in order to enter the cell.

2.2 Actions on the Muscle

As mentioned in section 2, testosterone is a potent anabolic hormone that stimulates muscle protein synthesis[13,15] and intramuscular amino acid uptake,[32] resulting in improved net protein balance.[33]

2.2.1 Effect on Androgen Receptor

Testosterone increases the AR in muscle cells and associated myonuclei and satellite cells.[33-36] The precise mechanism for this upregulation is not fully understood, but it is known that androgens increase the half-life of AR in cell culture suggesting a potential mechanism.[37,38] Several *in vivo* studies have shown that AR content is upregulated acutely by administration of pharmacological variants of testosterone in rats[35,36] and humans.[39] AR content continues to increase for several days after which the increased concentration of AR is maintained. It appears that after long-term continuous high circulating concentrations of testosterone from exogenous use, e.g. several months, the AR content returns to baseline in men,[33] whereas, cycling on and off exogenous testosterone, as many athletes who use anabolic steroids do, leads to a sustained long-term AR content increase in men.[34]

2.2.2 Importance for Normal Muscle Development and Maintenance

Testosterone is important for the development and maintenance of muscle mass in males. In boys, puberty is associated with increased circulating testosterone concentrations and accrual of muscle mass.[40] In contrast, sarcopenia (loss of muscle mass) has been associated with the decline in testosterone concentrations found with aging in men.[41-43] In older men, the effects of sarcopenia on muscle mass and function can be reversed by testosterone administration that returns circulating testosterone concentrations to within or near the normal physiological range.[33] Hypogonadism resulting from surgery (orchiectomy) or pharmacological testosterone deprivation therapy (the latter is commonly used with prostate cancer) also leads to reductions in muscle mass and function in adult males.[44-46] The importance of normal circulating concentrations of testosterone on muscle mass in women is less clear as a reduction in testosterone generally does not occur independently of reductions in other hormones such as estrogens (e.g. with menopause).[47] Despite these limitations, testosterone appears to be important for the maintenance of muscle mass in women. In women with muscle mass reductions resulting from hypopituitarism, testosterone administration that returns free testosterone to a normal concentration increased fat-free mass and muscle cross-sectional area.[48] Similarly, combined testosterone and estrogen administration to oophorectomized women resulted in increased lean mass; whereas, estrogen administration alone had no effect on lean mass.[49] In addition to these controlled clinical trials, there is substantial, yet anecdotal, evidence that exogenous supraphysiological doses of testosterone, as those used by some women body builders, have a very potent effect on muscle mass accretion in women.

In a series of experiments, Mauras and colleagues[15,50,51] examined the effects of testosterone on muscle protein synthesis and accretion in young men and prepubertal boys. Combined, these studies show that testosterone is vital for the development and maintenance of muscle mass via testosterone's stimulation of whole body protein synthesis and inhibition of proteolysis resulting in a net anabolic effect. In healthy prepubertal boys, acute testosterone administration increased protein synthesis, as measured by nonoxidative leucine disappearance as well as protein proteolysis, with an overall improvement in leucine and presumably protein balance.[50] In growth hormone (GH)-deficient prepubetal boys, testosterone reduced protein oxidation, as measured by leucine oxidation, but did not alter measures of protein synthesis; however, when 22-kD GH and testosterone were administered together, marked increases in protein synthesis were observed.[51] The authors concluded that a minimum concentration of GH was needed for the actions of testosterone; consequently, they suggested that GH had a permissive or synergistic effect on testosterone's promotion of protein synthesis. In accordance with the findings on testosterone administration, 10 weeks of administration of a GnRH analogue to young men (resulting in very low circulating testosterone concentrations) caused marked decreases in the rates of whole-body protein turnover and protein synthesis.[15] These reductions were manifested in decreased fat-free mass and muscle strength supporting the crucial role of testosterone in the maintenance of muscle mass and function in men.

Testosterone also has a stimulating effect on the production of other anabolic hormones. In

healthy, short-stature, prepubertal boys (Tanner stage 1), testosterone administration led to increases in circulating immunoreactive GH concentrations.[50] In GH-deficient prepubetal boys, testosterone administration increased circulating insulin-like growth factor (IGF)-I, although testosterone and 22-kD GH administered together caused an even greater increase in IGF-I.[51] Based on these findings, testosterone and 22-kD GH appear to have a synergistic effect on IGF-I release, although the effect of 22-kD GH alone was not examined. In mildly hypogonadal older men, testosterone treatment increased muscle IGF-I protein expression,[33] and in young men pharmacological testosterone deprivation reduced IGF-I messenger RNA (mRNA) expression (the nuclear-derived signal for IGF-I protein production at the ribosome) in muscle despite no changes in circulating immunoreactive GH and IGF-I concentrations.[15] Furthermore, cell cultures incubated with testosterone upregulate IGF-I mRNA expression in a dose-dependent manner.[52] Combined, these findings suggest that testosterone is required for muscle IGF-I production, and that this is a direct effect of testosterone independent of circulating immunoreactive growth hormone and IGF-I concentrations. However, a synergistic effect of testosterone and 22-kD GH on muscle IGF-I appears to exist. The recent identification of androgen response elements in the IGF-I upstream promoter region[52] provides further support for the importance of testosterone in muscle IGF-I production. Since IGF-I is also a potent anabolic hormone that directly increases anabolic gene transcription via the AKT/mammalian target of rapamycin (mTOR) pathway,[53] this influence of testosterone on muscle IGF-I production provides an additional mechanism by which testosterone can increase muscle protein synthesis and accretion.

3. Testosterone Response to Resistance Exercise and Training

The acute endocrine response to a bout of resistance exercise includes increased secretion of various catabolic (breakdown-related) and anabolic (growth-related) hormones. One of the primary anabolic hormones released in response to resistance exercise is testosterone; in fact, testosterone is believed to be the major promoter of muscle growth and subsequent increase in muscle strength in response to resistance training in men. In general, total testosterone and free testosterone are elevated directly following heavy resistance exercise in men, whereas, findings on the testosterone response to a bout of heavy resistance exercise in women are equivocal with both increases[54,55] and no changes observed.[56-58] The endocrine response for the days following resistance exercise is unclear. Häkkinen and Pakarinen[59] found a decrease of both total testosterone and free testosterone in men for the first 2 days following heavy squats (10 sets of 10 repetitions at 70% of 1-repetition maximum [1RM] or 20 sets of 1 repetition with 100% of 1RM), whereas, Koziris and colleagues[60] found no difference in total testosterone for the same time-points following whole-body circuit resistance exercise using universal gym machines (3 circuits of upper- and lower-body exercises with a 5RM load). This difference in findings could be due to the different exercise protocols used in the two studies and would suggest that the testosterone response for the days following resistance exercise is also specific to the resistance exercise protocol used. The protocol used by Häkkinen and Pakarinen,[59] especially the 10 sets of 10 repetitions, involved substantially more volume than the protocol used by Koziris et al.[60] Accordingly, the extent to which testosterone is acutely affected by resistance exercise largely depends on the selection among the acute programme variable domains for the exercise session.

Several of the acute programme variable domains interact with each other, so to investigate the effect of one variable domain on the testosterone response to resistance exercise other variable domains must often be manipulated. To reduce redundancy, studies in which this occurs will mainly be examined once and not repeated in sections for the other variable domains.

3.1 Men

In general, circulating total testosterone and free testosterone increase immediately after a bout of heavy resistance exercise in men and return to, or below, baseline within 30 minutes;[12,27,56,61-67]

however, the appearance and magnitude of these testosterone increases are greatly influenced by the selection among the 'acute programme variable domains' (intensity, number of sets, choice of exercise, order of exercise and rest period duration) for the exercise session.

3.1.1 Intensity

Intensity refers to the load or resistance used for a given exercise. There appears to be a relative intensity and volume threshold (total work performed; see section 3.1.3 below) that must be reached in order to induce a testosterone response. Comparing protocols with the same volume but different loads (4 sets of 6 repetitions at 52.5% of 1RM vs 3 sets of 6 repetitions at 40% of 1RM during concentric actions and 100% of 1RM during eccentric actions) for the bench press and squat exercises, Yarrow et al.[68] found that neither protocol produced an increase in testosterone. The intensity used in that study, with the exception of the eccentric action, was very low and this likely explains the lack of a testosterone response. Kraemer et al.[61] examined the effect of altering the intensity while keeping total work constant and found that when intensity was reduced, the testosterone response was attenuated. When the number of repetitions is kept constant, higher intensity and thus higher volume induces a greater testosterone response. Raastad et al.[69] showed that 3 sets of 6 repetitions for three lower-body exercises at 100% of 6RM but not at 70–76% of 6RM induced a significant increase in testosterone. Similarly, 5 sets of 10 repetitions with 10RM has been found to induce a significant testosterone increase; whereas, 5 sets of 10 repetitions with either 70% or 40% of 10RM did not affect testosterone concentrations.[56]

The findings on the effect of high relative intensity alone on the testosterone response are equivocal with both increases[70] and no changes found post-exercise.[59,64] Ten sets of 1RM in resistance trained men resulted in a significant acute increase in circulating testosterone;[70] however, 20 sets of 1RM in elite strength athletes did not induce an increase in testosterone.[59] Although speculative, the difference in findings could be attributed to the difference in rest periods (2 and 3 minutes, for the 10- and 20-set protocols, respectively) or the training level of the participants. In accordance with the findings by Häkkinen and Pakarinen[59] high relative intensity and low-moderate total work protocols (2, 4 or 6 sets of 5 repetitions with 80–88% of 1RM) did not induce a testosterone response.[64] In general, it appears that high relative intensity alone is not sufficient to induce a testosterone response if the total volume of the protocol is low; however, a relative intensity minimum threshold must be met, even with a high volume, to induce a testosterone response.

3.1.2 Number of Sets

This variable refers to the number of sets performed for each exercise in a resistance exercise session. When total volume is held constant, the number of sets does not appear to influence the acute testosterone response to resistance exercise.[61,71] Goto et al.[71] examined the effect of adding a 30-second rest period in the middle of each 10-repetition set. This added rest period essentially produced double the number of sets with half the repetitions but similar volume. Despite a lower metabolic demand (i.e. attenuated lactate response) the addition of the rest did not result in differences in the testosterone response. When changing the load while keeping volume constant, (and thus changing the number of sets) Kraemer et al.[61] found that no alterations in the resistance exercise-induced testosterone concentrations occurred. Similarly, 16 weeks of resistance training with all sets to either failure or not to failure, but the same volume and intensity (thus adding sets), did not alter resting testosterone; however, an increase in resting testosterone was found after 11 weeks.[72] It is difficult to ascertain the reason for this transient difference on the resting testosterone concentration, but it does suggest that subtle differences in adaptations can occur when sets are manipulated while keeping load and volume constant. It is possible that the high stress from performing each set to failure, which prevented a training-induced reduction in resting cortisol, led to a state of overreaching or mild overtraining and thus prevented a transient anabolic adaptation manifested in elevated testosterone concentrations. This possibility is supported by the finding that IGF-I concentrations were reduced with the

sets to failure condition, although performance did not appear to be affected in this group.

3.1.3 Volume

Volume refers to the total work performed and is often used in the context of resistance exercise to mean (set × number of repetitions × intensity). Using this definition, volume is a function of several different acute programme variable domains and is therefore not considered an independent acute programme variable domain. However, manipulating volume by changing several of its constituents can significantly affect the hormonal response; this potent effect of volume warrants its inclusion in this review. There appears to be a threshold of volume or metabolic demand that must be reached before increases in testosterone are observed. Ratamess et al.[66] showed that 6 sets, but not 1 set, of 10 repetition squats significantly increased total testosterone post-exercise. The metabolic demand of the 1-set protocol was relatively low, manifested by an only modest increase in lactate; whereas the 6 sets produced a large increase in lactate, suggesting a high metabolic demand. The requirement for a high metabolic demand and not just high intensity for an increase in testosterone post-exercise was shown by Häkkinen and Pakarinen.[59] Twenty sets of 1RM resulted in no change in testosterone, whereas 10 sets of 10RM resulted in a large increase in free and total testosterone. The lactate response was modest (~4 mmol/L) with the high-intensity protocol but substantially larger (~15 mmol/L) with the high volume protocol supporting the hypothesis that a large metabolic demand is needed to induce a testosterone response. Furthermore, an examination of various combinations of sets and repetitions found that, in general, a higher volume created a greater testosterone response.[64] In that study,[64] the threshold for a testosterone response appeared to be based more on metabolic demand than on volume *per se*; however, the study did not attempt to establish this threshold.

3.1.4 Choice of Exercise

Choice of exercise refers to the specific exercise chosen (e.g. power clean), the equipment used (e.g. machine or free weight), and how the exercises are performed (e.g. type of muscle action, velocity of movement). One of the major determinants for the occurrence of a testosterone increase with resistance exercise is the muscle mass used. Involvement of a small muscle mass, even when exercised vigorously, does not elevate testosterone above resting concentrations.[73] Exercise selection, therefore, significantly influences the testosterone response to a resistance exercise session. Bilateral knee extension alone[74] or the combination of unilateral knee extension and leg press[75] performed with a 5–10RM load does not induce a testosterone response. Similarly, unilateral biceps curls alone do not induce a testosterone response, but the addition of bilateral knee extensions and leg press to the biceps curl protocol results in a significant testosterone response.[76] When resistance exercise induces an increase in testosterone, the magnitude of that increase is also affected by muscle mass involvement; a jump squat protocol increases testosterone concentration more than a bench press protocol performed by the same participants (15% vs 7% for the jump squat and bench press, respectively).[77] Similarly, exercises such as the squat[27,66,78] and Olympic lifts,[79] that involve a large muscle mass, produce larger elevations in testosterone compared with smaller muscle mass exercises.[76,80,81] Larger muscle mass involvement allows for greater total volume, which helps to explain the importance of muscle mass involvement in inducing a testosterone response to resistance exercise. As described in section 3.1.3, the total volume of work has important implications for the appearance and magnitude of the testosterone response to resistance exercise. The effect of exercise modality (free-weight or machine exercises) on the testosterone response does not appear to have been investigated directly, but both modalities can produce substantial increases in testosterone when a high load and volume is used.

Only a few studies have investigated the effect of modes of muscle contraction on the acute testosterone response to resistance exercise.[80,82,83] When the same relative intensity is used, there does not appear to be a difference in the testosterone response between concentric and eccentric

exercises.[80] Durand et al.[82] found that concentric and eccentric exercise protocols using the same absolute intensity produced an increase in testosterone with no difference between modes of contraction. Despite the lack of a significant difference between modes of contraction, the concentric condition produced almost twice as large an increase in testosterone compared with the eccentric condition, suggesting that mode of contraction can affect the testosterone response to resistance exercise.[82] When the same relative load is used, free testosterone increases similarly following concentric and eccentric muscle action resistance exercise.[83] It seems likely that the potential difference in the testosterone response between modes of contraction using the same absolute load, as presented by Durand and colleagues,[82] might be because the maximal force capability is higher for eccentric muscle actions than for concentric muscle actions[84] and as a consequence, the relative intensity was lower during the eccentric exercises.

In recent years, whole-body vibration (WBV) has resurfaced as an alternative mode of resistance training. The hormonal response to WBV has been examined by a few studies with both no effects[85-87] and elevations found for testosterone.[88] Ten sets of 1-minute isometric half squats during WBV did not affect salivary testosterone concentrations;[85] similarly, neither 25 minutes of standing WBV[87] nor 6 sets of 8 repetitions of unloaded squat (30-second per set) during WBV affected circulating testosterone concentrations.[86] Adding WBV to a protocol consisting of 6 sets of 8RM squats did not affect the post-exercise increase in testosterone compared with the squat protocol alone; furthermore, this response was not altered by 9 weeks of training using WBV and squats.[86] In contrast to these findings, Bosco and colleagues[88] found that 10 sets of 1-minute isometric squats during WBV significantly increased circulating testosterone, although the increase was only modest (1.6 nmol/L, equal to ~7%). It appears that WBV has no or only a limited effect on testosterone. More research is needed to firmly establish the effects of WBV on the acute testosterone response to exercise.

3.1.5 Order of Exercise

The order of exercise refers to the sequence of exercises within an exercise session; this order affects the power output and the number of repetitions that can be completed for each exercise.[89] The order of exercise can also affect the timing of the hormonal response to resistance exercise. Large muscle mass exercises are needed to acutely increase circulating testosterone concentrations and as a result when large muscle mass exercises are performed in the beginning of an exercise session, the muscle used during subsequent exercises will be perfused with an elevated testosterone concentration. The importance of elevated anabolic hormones including testosterone was shown by the finding that when the biceps is trained after 4 sets of leg press, it hypertrophied significantly more compared with training of the biceps alone.[76] It remains to be determined if altering the order of exercises while keeping the load and repetitions constant, affects the post-exercise testosterone response.

3.1.6 Rest Period Duration

The duration of rest periods refers to the time (minutes or seconds) between each set and each exercise. Rest period duration can substantially affect the metabolic demand of a bout of resistance exercise as evident by the lactate response[61] and the average oxygen consumption[90] for the session. It is well established that increased metabolic demands augment the response of certain other hormones, such as immunoreactive GH,[61] yet this effect has not been shown for testosterone. Only a single study appears to have isolated the effect of rest period duration on the testosterone response to resistance exercise. That study observed that only in the context of moderate loads (10RM) with high volume (~60 000 J) did short rest (1 minute) result in a significantly larger testosterone response compared with longer rest (3 minutes).[61] Ahtiainen and colleagues[91] reported no effect of rest period duration (2 vs 5 minutes) on the testosterone response to resistance exercise; however, the protocols used for each rest period duration condition differed slightly in the load and sets used making direct comparisons difficult. It appears that with different combinations

of load and volume, rest period can affect the acute resistance exercise-induced testosterone response. Synergistic integration among resistance, rest and volume therefore likely exists, but the magnitude of each required for the different testosterone response patterns remains to be determined.

3.2 Women

The biological mechanisms for a potential exercise-induced increase in testosterone might be different in women compared with men. Women do not have Leydig cells and Kvorning et al.[12] have shown that the Leydig cells are likely involved in the acute resistance exercise-induced increase in testosterone in men. An increase in free or total testosterone for women has been found in some studies[54,55,62,92] but not all studies.[56,58,93] One might speculate that such equivocal findings are due to differences in the selections within each acute programme variable domain; however, this has not been substantiated.

Only a few studies have directly examined the effect of specific acute programme variable domains on the testosterone response to resistance exercise in women; however, these studies have found no acute elevation in testosterone post-exercise. Linnamo et al.[56] demonstrated no changes in total testosterone following 5 sets of 10 repetitions each of sit-ups, bench press and leg press using three different loading conditions: maximal (10RM), submaximal (70% of 10RM) and explosive (40% of 10RM). In men, the same maximal load condition led to a significant increase in total testosterone.[56] Similarly, Kraemer et al.[58] showed that with heavy resistance exercise altering rest period duration or load while keeping total volume constant did not result in post-exercise testosterone concentrations above baseline in women.

Although no acute changes following exercise were found, the simultaneous manipulation within several of the acute programme variable domains has been shown to affect resting total testosterone following long-term resistance training in women.[93] A low-volume, single-set circuit programme produced only a modest increase in resting testosterone after 12 weeks, but resting testosterone returned to baseline at 24 weeks of training. In contrast, a periodized high-volume, multiple-set programme produced a large increase in resting testosterone at 12 weeks and an even larger increase at 24 weeks of training. Thus, the training programme design significantly affected the magnitude and sustainability of the increase in resting testosterone concentration.

It has been reported that in men a GnRH analogue (goserelin), which suppresses circulating LH and thus Leydig cell function resulting in castrate concentrations of testosterone, prevents an acute resistance exercise-induced increase in total and free testosterone.[12] Thus, it appears that the Leydig cells are responsible for acute increases in testosterone following resistance exercise, and this would explain the lack of consistent findings for the testosterone response to resistance exercise in women. The acute increase in testosterone, especially free testosterone, following resistance exercise reported in some studies could originate as a byproduct of cortisol production. Adrenocorticotropic hormone, which stimulates production and release of cortisol, also causes release of testosterone from the adrenal cortex.[94] Adrenocorticotropic hormone concentrations increase in response to heavy resistance exercise,[95] which could lead to a greater adrenal production and release of testosterone. Considering that free testosterone is a very small part of total testosterone (0.5–2%), a small increase in free testosterone might not be detectable in total testosterone concentration analysed using standard enzymatic procedures. None of the studies that showed an increase in testosterone included measurements of the adrenocorticotropic hormone response to resistance exercise, and only one study included measurements of cortisol; Copeland et al.[55] found that both testosterone and cortisol were elevated compared with control following resistance exercise. Alternatively, the resistance exercise-induced increases in testosterone could simply be due to a reduction in plasma volume, which could cause an increase in circulating testosterone concentration without a change in the amount of testosterone in the circulation. It is also possible that statistical limitations due to the relatively low number of subjects in some of these

studies might negate findings of significant increases due to the potential variance involved in women's response patterns.

3.3 Effect of Age

Age significantly affects circulating testosterone concentration. Children have low concentrations of testosterone until puberty when testosterone increases markedly in boys and to a minor extent in girls.[96] Aging beyond 35–40 years is associated with a 1–3% decline per year in circulating testosterone concentration (1.6% in total and 2–3% in bioavailable testosterone) in men.[97] This reduction can eventually lead to very low resting concentrations of circulating testosterone, a condition that has been termed andropause.[98] In women, circulating testosterone concentrations also gradually decline until menopause after which a 60% reduction is found within 2–5 years.[47]

The testosterone response to resistance exercise is also greatly affected by age. Boys do not experience an acute increase in testosterone in response to resistance exercise; even after the onset of puberty when resting testosterone is increased in boys, they appear to experience no or only a minor resistance exercise-induced increase in testosterone.[63,99] Following the same resistance exercise session, testosterone increased in college-aged men but not in high school-aged young men.[100] Similarly, Pullinen et al.[63,99] showed that in contrast to resistance-trained men, there was no or only a minor increase in testosterone following resistance exercise in 14- and 15-year-old boys, respectively, who had been engaged in resistance training for at least 1 year. This lack of exercise-induced increase in testosterone in boys existed even though there was no difference in resting testosterone concentrations between the men and boys.[63,99] Although speculative, the reason for this limited testosterone response to resistance exercise in teenage boys might be due to an inability of the testis to quickly increase testosterone release or a lack of sufficient metabolic stimulus (volume) from the exercise session based on the relatively low maximal strength in this population. This notion is supported by the finding that junior weightlifters (14–18 years of age) with more than 2 years of weight-lifting experience produce a greater acute testosterone response than those with less than 2 years of experience.[79]

In older (≥59 years)[27,62,78,101] and middle-aged (38–53 years)[62,81,101] men a bout of resistance exercise can elicit a significant elevation in circulating total and free testosterone, but the magnitude of this elevation is generally smaller compared with that in younger (20–30 years) men.[27,78,81,101] This attenuated exercise-induced increase is especially apparent for free testosterone. The discrepancy between findings for free testosterone and total testosterone could be due to the increased concentrations of SHBG and reduced concentrations of albumin found with aging.[102,103] The findings for training effects on the acute testosterone response to resistance exercise in older men are equivocal with both no effects and augmented responses found. A 10-week periodized strength-power training programme led to increased pre-exercise free testosterone and post-exercise total testosterone concentrations in ~60-year-old men with no changes found for ~30-year-old men undergoing the same training programme.[78] In contrast, Häkkinen and colleagues[62] found no changes in the acute pre- or post-resistance exercise testosterone response following 6 months of strength training in older (~70 years old) and middle-aged (~40 years old) men. Both studies,[62,78] however, found that there were no changes in testosterone concentrations of older men at rest (i.e. not immediately pre-exercise) after the resistance training period. It is difficult to speculate on the cause of the discrepancy in the findings for the acute testosterone response to resistance exercise, but it is possible that an anticipatory response was present following training in the study by Kraemer et al.[78]

In middle-aged (~40-year-old) and older (~60- to 70-year-old) women who are untrained, total and free testosterone do not change acutely in response to a high (5 sets of 10RM in the leg press)[62,104] or moderate (1 set of 13 exercises at 80% of 1RM)[105] volume resistance exercise session. Long-term strength training does not appear to change resting total and free testosterone[62,104-107] or post-exercise total testosterone concentrations in response to high[62,104] or

moderate volume.[105] One study, however, found that in recreationally trained 19- to 69-year-old women, total testosterone increased acutely following a high-volume (3 sets of 8 exercise at 10RM and 1 minute rest between sets) resistance exercise session and that this increase was not affected by age.[55] Findings on the effect of training on the acute free testosterone response to resistance exercise in aging women are equivocal. In both middle-aged and older women, an acute increase in free testosterone following resistance exercise (5 sets of 10RM in the leg press) after 6 months of resistance training has been observed.[62] A different study by the same authors[104] using similar older female populations and the almost identical acute resistance exercise protocol, (2 minutes instead of 3 minutes of rest between sets) found that 21 weeks of strength training did not change the acute free testosterone concentrations following a bout of resistance exercise. Based on these findings, it appears that the testosterone response to resistance exercise and training in aging women is similar to that for younger women. In both younger and older women, resistance exercise can induce an acute increase in circulating testosterone; however, the selection among the acute programme variable domains required for this increase to occur has not yet been fully determined.

3.4 Effect on Androgen Receptor

Only a limited number of studies have examined the acute AR response to a bout of resistance exercise in men;[12,65-67,74,92,108] only one study appears to have been conducted in women.[92] From the studies in men combined with the findings from animal research,[109,110] it appears that the AR concentration is initially reduced acutely following a bout of resistance exercise, but that AR is upregulated during the later stages (several hours after exercise) of recovery from resistance exercise. The timeline for this AR down- and upregulation has not been fully elucidated. Ratamess et al.[66] and Vingren et al.[92] found that in young resistance-trained men 6 sets of 10 repetitions in the squat exercise with 2 minutes of rest between sets resulted in a significant decline in AR 1-hour post-exercise. Similarly, Lee et al.,[35] using a male rat model, found that overload ablation caused a decrease in AR 24-hours post-overload introduction. In contrast to these findings, Kraemer and colleagues,[67] using a similar population to Ratamess et al.[66] and Vingren et al.[92] but a slightly different resistance exercise protocol (4 sets of 10 repetitions of squat, bench press and shoulder press and row with 2 minutes of rest between sets), found that AR increased 1-hour post-exercise when subjects ingested either water or a carbohydrate-protein drink immediately after exercise. The increase in AR was much greater with the carbohydrate-protein drink compared with the water ingestion condition suggesting a potent effect of nutrition on the AR response to resistance exercise.[67] The differences in AR expression between the studies in the fasted conditions (water) were observed despite similar testosterone responses and involvement of the muscle sampled for AR. This indicates that other variables such as time from onset of exercise or testosterone exposure might affect the AR response. Finally, Spiering et al.[74] recently found that in untrained men, AR was upregulated 3 hours post-resistance exercise only when the exercise bout produced an increase in circulating testosterone. Although not considered resistance exercise, it is also worth noting that strenuous swimming has been shown to upregulate AR acutely (within hours) following exercise.[111] Combined, these studies suggest that after an initial reduction in AR following exercise, an acute upregulation of AR in the hours following a bout of resistance exercise in men occur, although the timeline for the events in this response is uncertain. The only finding for women suggest that the AR response is similar among men and women except that the initial reduction in AR is present 10-minutes post-exercise and AR returns to baseline by 70-minutes post-exercise.[92]

Findings for AR during the later stages of recovery from resistance exercise are more consistent. Forty eight hours following a bout of resistance training AR mRNA is upregulated.[65,108] However, Willoughby and Taylor[65] did not find an increase in AR protein content until 48 hours after two consecutive resistance exercise sessions

separated by 48 hours. In animal models, electrical stimulation[110,112] and overload ablation[109] result in an acute upregulation of AR during the later stages of recovery (several days after the initial overload stimulus). Collectively, these studies suggest that the acute AR response to resistance exercise includes a stabilization phase followed by an acute initial downregulation after which an upregulation of AR to above baseline concentrations occur. Despite the few studies on the acute AR response to resistance exercise, it appears that factors such as exercise volume and nutrient intake affect this response. Ratamess et al.[66] showed that a single set of 10 repetitions in the squat exercise did not alter AR 1-hour post-exercise. This was mirrored by limited changes in circulating lactate and hormonal concentrations suggesting that a minimum of volume is needed to induce AR changes in response to resistance exercise. Post-exercise ingestion of a drink containing protein and carbohydrate led to an increase in AR 1-hour post-exercise with or without L-carnitine supplementation.[67] Interestingly, it has also been demonstrated that when a protein and/or carbohydrate drink is ingested before or after resistance exercise, the increase in testosterone is attenuated during exercise, and the reduction in testosterone during recovery is augmented compared with a placebo condition.[67,113,114] The authors of these studies suggested that increased testosterone uptake by the AR might account for this attenuated testosterone response.

4. Conclusions

As a hormone, circulating testosterone signalling resides within a multivariate system of anabolic signals for many different target tissues through the body, and the exact role of testosterone in the temporal timeframes of a resistance training programme are hard to pinpoint. Yet, dismissal of its anabolic role in the human body due to a lack of a simple correlation or comparison of punctual circulating testosterone concentrations with variables that have accumulated over time with training (e.g. muscle size, strength) is over-simplistic at best and understates the importance of this hormone to the physiology of adaptational mechanisms in the human body to exercise stressors. The interaction of testosterone with a host of receptors on different tissues and the resulting signalling processes are vital to human health and performance. The increase in testosterone found in men is important for the resistance exercise-induced adaptations. The importance of testosterone for adaptations to resistance exercise in women has not been substantially examined, but it appears that testosterone plays only a minor role.

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