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REVIEW ARTICLE

Effects of endurance exercise on the reproductive system of men: The "exercise-hypogonadal male condition"

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ABSTRACT. An increasing number of investigative research studies point to participation in endurance exercise training as having significant detrimental effects upon reproductive hormonal profiles in men. Specifically, men chronically exposed to this type of exercise training exhibit persistently reduced basal (resting-state) free and total testosterone concentrations without concurrent LH elevations. Men displaying these symptoms have been deemed to exhibit the "exercise-hypogonadal male condition". The exact physiological mechanism inducing the reduction of testosterone in these men is currently unclear, but is postulated to be a dysfunction (or perhaps a readjustment) within the hypothalamic-pituitary-testicular regulatory axis. The potential exists for the reduced testosterone concentrations within exercise-hypogonadal men to be disruptive and detrimental to some anabolic-androgenic testosterone-dependent physiological processes. Findings on this point are limited, but do suggest spermatogenesis problems may exist in some cases. Alternatively, reductions in circulating testosterone concentrations could have cardiovascular protective effects and thus be beneficial to the health of these men. Present evidence suggests the exercise-hypogonadal condition is limited to men who have been persistently involved in chronic endurance exercise training for an extended period time (i.e., years), and it is not a highly prevalent occurrence (although, a thorough epidemiological investigation on the topic is lacking in the literature). Many questions regarding the male reproductive endocrine adaptive process to exercise training still remain unanswered, necessitating the need for much further investigation on the topic, especially with respect to the exercise-hypogonadal condition.

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INTRODUCTION

Men who participate in endurance exercise events (e.g., marathons) perform a large volume of exercise training (1-4) on a regular basis. Case in point, it is not uncommon for a competitive marathon runner to complete 150 to 200 km of intensive running per week as part of their normal preparatory training regime (2, 3). This can be the equivalent of 10-20 h a week in exercise time. Exercise training to this extent can result in many positive physiological adaptations that are highly beneficial to the athlete, such as, an enhancement of the maximal cardiac stroke volume and maximal cardiac output, increased blood volume and hemoglobin concentrations, increased maximal arterial-venous oxygen differential, increased erythrocyte number, decreased levels of stored adiposity, improved thermoregulatory capacity, and increased skeletal muscle mitochondrial density (3-5). These types of changes in physiological parameters result in the potential for a greatly increased human performance capacity. Yet, exercise training to this extent can also place an incredible amount of stress and strain on the sportsman's body and result in unwanted physiological responses and an increased risk certain health problems – such as, the "Overtraining Syndrome" condition, which can completely compromise the ability of a sportsman to perform adequately (2, 4, 5). Additionally, exercise training to this degree greatly enhances the likelihood of musculoskeletal trauma or injury occurring (1, 4, 5).

One physiological system in the body that is extremely sensitive to the stress of exercise training is the neuroendocrine system (4-6). This seems particularly true for the components of the system associated with the control and regulation of reproductive function (7). During the last several decades, an increasing number of investigative research studies have pointed to how chronic exposure to endurance exercise training can result in the development of a dysfunction within the reproductive components of the neuroendocrine system (5, 8-11). The vast majority of these research studies have concentrated upon women who are involved with exercise-sport and its impact on reproduction issues of the menstrual cycle and fertility (12-14). However, beginning in the 1980s investigators began to examine how exercise training (15), primarily endurance-type, affects the reproductive neuroendocrine system in men too. A growing but limited number of investigations have been conducted on the topic since that initial work took place.

Research in exercising men demonstrates the existence of a select-group who, through their chronic exposure to endurance exercise training, have developed alterations in their reproductive hormonal profile, i.e. persistently low basal resting testosterone concentrations. Specifically, the majority of these men exhibit clinically "normal" concentrations of the hormone testosterone, but the concentrations are at the extreme low end of normal range; and, in some cases do reach sub-clinical status. The key health consequences of such hormonal changes are increased risk for abnormal spermatogene-

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sis, male infertility problems, and compromised bone mineralization (16, 17). The current state of the evidence thus far, suggests the prevalence of such health problems seems low, but the investigative studies examining this condition and its consequences are few in number (16, 19). Regrettably, a thorough large-scale epidemiological investigation on the health consequences of the low testosterone levels in this select-group of men is lacking in the literature.

The specific terminology used to refer to these "endurance exercise-trained men with low basal resting testosterone" has not been universally agreed upon. In 2005, Hackney and associates proposed the use of the phrase the "exercise-hypogonadal male" as a label for this condition (18). This is the terminology used in the discussion throughout this article.

This review article presents a brief synopsis discussion of the major published investigative research studies addressing the neuroendocrine and physiological characteristics associated with the "exercise-hypogonadal male condition". The aim of the review is to address how endurance exercise training affects the male reproductive neuroendocrine system to induce hypogonadal-like conditions, resulting in suppressed circulating testosterone concentrations, and what mechanisms may in turn be bringing about the condition. This review article is intended as an introduction to the overall topic. A more in-depth and lengthy treatise dealing with the topic can be found in a combination of selected references (e.g. 7, 16, 19).

BASAL-RESTING RESPONSES

Investigative research studies examining the "exercise-hypogonadal male condition" topic have principally been either of a retrospective design approach (i.e., essentially cross-sectional and involved selecting men who have been exercise training on their own for some period of time), or a prospective design approach (i.e., longitudinal, in which men are subjected to exercise training by the investigators for some period of time). Each of these types of research design has strengthens and weakness, this section of the article discusses findings from both research design approaches (18).

Retrospective-based comparative research investigations have consistently reported significantly lower testosterone concentrations in exercise-hypogonadal men. In these studies, single isolated basal blood samples (usually morning) have been obtained and analyzed. The subjects of these studies have been almost exclusively distance runners who had been involved with exercise-sports training for a number of years (>1 up to 25 yr). Testosterone concentrations in these exercise-hypogonadal men have been only 40-75% of the concentration levels found in the age-matched, sedentary control subjects used in these studies (9, 20-27).

It is well known that many hormones, including testosterone, can display seasonal variation (28). Also, sportsmen vary their training volume seasonally to incorporate the periodization approach to training and competing (5, 29). This seasonal variation in hormones, as well as adjustments in training volume, could interact to complicate the interpretation of hormonal profiles in sportsmen. Figure 1 displays an illustration of the degree of variance which could be seen in testosterone for men involved with exercise training (23). Research by Gulledge et al. addressed this seasonal issue in exercise-hypogonadal men. They reported that the low basal testosterone findings are highly reproducible and not just an aberration of the yearly season or the sportsmen's seasonal training regime (30).

There are also retrospective investigations where multiple basal blood specimens were collected frequently within the same day, every 20 or 30 min for 4 to 8 h periods, in exercise-hypogonadal men and compared to control sedentary subjects. Results are nearly identical to those of the single blood sampling studies noted above; that is, basal testosterone concentrations of the exercise-sports trained subjects were typically reduced and represented only 60-80% of the values found in age-matched, control sedentary men (21, 31, 32).

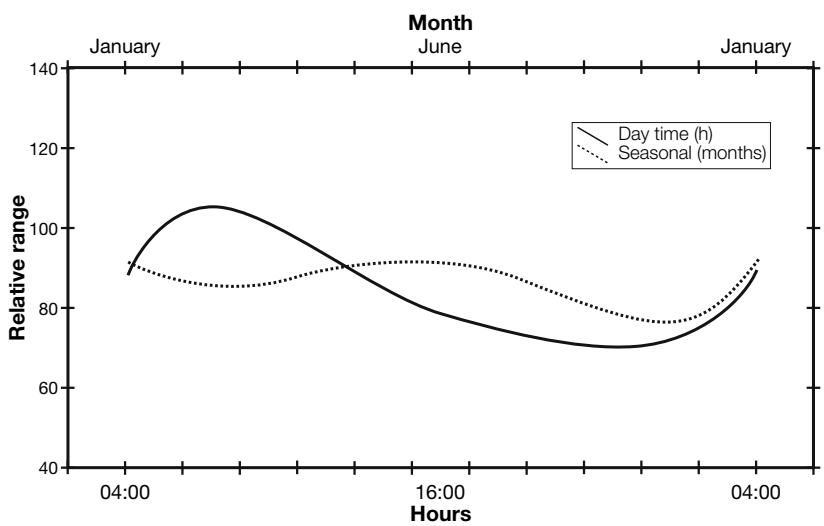

Fig. 1 - *The daily and seasonal variation in testosterone (relative change as compared to typical resting levels) seen in men involved with chronic exercise training. The figure is based upon accumulative data provided by reference (23).*

Published investigative research studies using prospective approaches also support the occurrence of low testosterone concentration existing in endurance exercise-trained men. In investigations using this design methodology, basal blood samples have been collected repeatedly over weeks or months while exposing subjects to endurance exercise (sports) training regiments. The findings from these prospective studies, however, have not been as unanimous or consistent as the retrospective-based findings. Several investigations have revealed significant reductions (e.g., decreases of 20-40% from pre-training regime concentration levels) in basal testosterone concentrations following 1 to 6 months of intensive training (33-39). Other investigations, conversely, report no significant change in basal testosterone concentrations following approximately 2 to 10 months of exercise training (40-45). Differences in the initial level of physical fitness (i.e., training status) of the subjects, or the exercise training dosage administered within the individual research studies may conceivably account for the discrepancy in the findings. It is also likely that many of these prospective investigations were conducted for too short a period of time (i.e., months, whereas in the retrospective studies the men with low basal testosterone concentration have been exercise and sports training in many cases for years).

Exercise-hypogonadal men also display other reproductive hormonal abnormalities, besides just that associated with testosterone. The most frequent other hormonal profile abnormality reported involves the lack of a significant elevation in basal LH in correspondence with the substantially reduced testosterone (i.e., reflective of hypogonadotrophic-hypogonadism characteristics) (15, 20, 21, 46). These LH abnormalities involve not only concentrational differences, but in some cases luteinizing pulse characteristics disparities, although this is not a universal finding (23, 31). Furthermore, some cases of significant reductions in basal, resting PRL concentrations have been reported in these men (15, 20). These findings of altered basal PRL and LH alterations in exercise-hypogonadal men have been interpreted by some researchers as indicative of a dysfunction existing within the hypothalamic-pituitary-testicular axis (16, 19). That is, a potential compromise exists in the operation and responsiveness of the regulatory axis. These types of PRL and LH findings in exercise-hypogonadal men have been reported in both retrospective and prospective design investigations involving either single or multiple daily blood sampling protocols (9, 15, 20, 21, 46, 47).

As noted earlier, these reproductive hormonal findings have been primarily found in sportsmen involved in endurance exercises training (for example, marathon distance runners, cyclists, and tri-athletes). It is highly unlikely though, that these hormonal alterations are limited to just these categories of exercise-sport groups alone. In fact, some evidence has shown such findings exist even in resistance-trained sportsmen (48). The high occurrence of such finding in endurance exercise sportsmen most likely represents the tendency of researchers to center their attention on these groups, following the lead of early investigative studies conducted on this topic. As exercise science researchers expand their endocrinological studies to include other exercise-sport groups involved with endurance exercise training, it is highly likely that comparable findings will be revealed.

STUDIES EXAMINING MECHANISMS OF EXERCISE-HYPOGONADISM DEVELOPMENT

A number of investigative research studies have not only described the existence of the exercise-hypogonadal condition, but also attempted to elucidate the mechanism of the proposed hypothalamic-pituitary-testicular axis dysfunction in these men. These investigations have focused on examining whether the dysfunction exists within the hypothalamic-pituitary (central mechanism component) or in the testes (peripheral mechanism component) of the regulatory axis.

Central mechanism research has focused upon alterations observed in PRL and LH and possible production and, or secretion abnormalities with these hormones. Such alterations in PRL and LH production-secretion have been an area of extensive research in exercising women who develop reproductive dysfunctions (i.e., amenorrhea) (12, 14, 49). Thus, to a great extent the male research investigations have been modeled after that which has been done on females for a number of years (12, 14, 50, 51).

Exercise-hypogonadal men have been shown to have attenuated secretion of LH following exogenous GnRH challenges (44, 46, 52, 53). This suggests that perhaps there might be the development of some type of GnRH resistance (e.g., reduced receptor sensitivity) or compromised LH production capacity at the anterior pituitary. Interestingly, as noted earlier, results are ambiguous as to whether LH pulsatile characteristics (i.e., pulse frequency and amplitude) are consistently affected in exercise-hypogonadal men (9, 20, 21, 31, 34).

Alternatively, some exercise-hypogonadal men have a greatly augmented PRL secretion to an exogenous stimulus (drugs) (52). Boyden et al. (51) have shown a similar finding in women involved with endurance exercise training. Also, some exercise-hypogonadal men are reported to have an exaggerated PRL response to exercise sessions (20). This last finding has also been shown in some exercise-trained men with normal resting testosterone levels as compared to sedentary men when doing identical exercise (22). The hormone PRL presents an interesting paradox in reproductive physiological function. Small amounts of the hormone seem necessary to work synergistically at the testis with LH, while excessive circulating levels disrupt both central and peripheral aspects of the hypothalamic-pituitary-testicular axis (54-56). Some researchers speculate that any "stressful" situation might provoke disproportionate PRL responses in exercise-hypogonadal men and this in-turn ultimately promotes a reproductive axis disruption (8, 19, 33). However, this hypothesis needs to be thoroughly investigated in future research work.

Leptin is an adipocyte-released hormone associated in part with communicating to the hypothalamus satiety (i.e., appetite) and energy reserves status (57). It also has been linked to reproductive function in men; and, androgens such as testosterone have suppressive effects on leptin levels (57). Acute exercise is known to transiently alter

testosterone as well as leptin (58, 59). Furthermore, chronic exercise training can impact upon resting leptin concentrations, independent of just changes in body adiposity content (60). Interestingly, however, apparently no research studies to date have examined whether the leptin concentrations in exercise-hypogonadal men are normal or not. Ghrelin is another hormone associated with appetite-regulation. It is released by the endocrine cells within the gastrointestinal tract (61). Newly immerging experimental evidence, coming mostly from animal studies, suggests that ghrelin may function as a metabolic modulator of the gonadotropic axis, with predominant inhibitory effects in line with its role as signal of energy deficit (62). These effects may include inhibition of LH secretion as well as partial suppression of normal puberty onset (62). Acute and chronic exercise has been shown to influence ghrelin concentration levels (63). Yet, as with leptin, no research has apparently examined whether ghrelin concentrations in exercise-hypogonadal men are normal or if a relationship exists relative to their condition. It is necessary for future research studies to examine what, if any, linkage or role leptin and ghrelin may have with the status of, or development of the exercise-hypogonadal condition.

Peripheral mechanism research investigations have centered on alterations in the responsiveness of the testes to exogenous stimuli (i.e., LH or hCG challenges). Evaluations of testicular ability to produce and secrete testosterone in exercise-hypogonadal men to date have been contradictory. Some investigations suggests testicular testosterone steroidogenesis is normal (46, 52), while some suggest it is impaired to some marginal degree when challenged with an exogenous stimuli (53, 64, 65). It is important to note, however, exercise training has been definitively demonstrated to compromise testicular enzymatic activity in anima-based research (66).

In a related manner, research reveals acute pharmacological or pathological-related increases in the stress hormone cortisol is associated with decreased circulating testosterone (54, 67, 68). It has been hypothesized that such stress hormone changes serve as a potential mechanism for the low testosterone potentially in exercise-hypogonadal men (8, 69). Specifically, because a single, acute exercise session at moderate-to-high intensity (60% or greater of an individuals maximal aerobic capacity) can produce large transient increases in circulating stress hormone levels (70). Such hormonal increases on a daily basis are common within a training regime and thus could bring about the observed reductions in testosterone *via* the inhibitory actions of the stress hormone at the testes (68-71). A recent exercise investigation by Daly et al. supports this concept, with respect to cortisol inhibition actions (72). Additionally, it is interesting that Putnam et al. has demonstrated the hypothalamic-pituitary-adrenocortical axis has enhanced activity in normal men who undergo an induced hypogonadism (73). Collectively, these findings are compelling and fascinating. They are nevertheless circumstantial in nature and much further experimental research is necessary before definitive cause and effect conclusions can be drawn about such a cortisol-related mechanism.

To summarize, the present evidence indicates that either central or peripheral mechanisms (or perhaps both) within the reproductive regulatory axis can be influenced by endurance exercise training in men exhibiting the exercise-hypogonadal condition. More mechanistic-based research studies are warranted to resolve the current ambiguities in the findings with respect to this issue.

HEALTH CONSEQUENCES OF THE EXERCISE-HYPOGONADAL CONDITION

Testosterone and other similar androgenic hormones help to promote and regulate a myriad of physiological processes at the systemic, organism, tissue, cellular, and molecular levels (56, 74). Evidence suggests the development of low resting testosterone concentrations in men doing endurance exercise training have some detrimental effects on certain select testosterone-dependent processes and are connected to some health concerns. Unfortunately, to date, only a very few investigations have systematically studied the issue of the health consequences of developing the exercise-hypogonadal condition. A particularly significant finding has been a compromised spermatogenesis status in exercise-hypogonadal men (16, 48, 75-78). For example, one extremely well-controlled study on this topic was performed by Arce et al. (48). These investigators demonstrated that significant spermatogenesis problems such as reduced sperm density, decreased motility, increased abnormal morphology, and decrease penetration rate (*in vitro*) existed in exercise-hypogonadal men. Such findings, however, are not completely universal in the literature (43). In a related fashion, a lowered sex drive has also been reported in some exercise-hypogonadal men, but a direct cause-and-effect linkage between a lower sex drive and lower testosterone has not been demonstrated (64, 76, 79-82). Other facts may be affecting the libido status of these men (e.g., overall fatigue and psychological stress) (83, 84). Thus, this is an additional area where more clinical-based research is necessary and warranted in the next few years.

One concern raised by some investigators is the issue of the impact of low testosterone concentrations on bone mineral content in exercise-hypogonadal men (17, 85) [i.e., modeled after the health concerns found in exercising women (13, 14, 49, 86)]. Several compelling case study reports have found exercise-hypogonadal men to have excessively low overall bone mineral density levels (76, 87, 88). In a large cross-sectional study, Hetland et al. showed male distance runners do have lower bone mass and higher rates of bone turnover than sedentary controls (89). However, these investigators found no relationship between testosterone levels and their measured bone characteristics. In contrast, MacDougall et al. and Maimoun et al. found endurance-trained men (some with the exercise-hypogonadal condition) had normal bone mineral content (90, 91). Furthermore, Zittermann et al. showed that exercise-hypogonadal men actually have higher calcitriol concentrations and higher calcium absorption rates (92). Thus, while a concern, so far no large-scale experimental study findings currently support that bone mineral content is severely compromised in exercise-hypogonadal men as is seen in amenorrheic (hypogonadal) women who are sports participants (14, 49, 86).

Table 1 - *The table summarizes the common characteristics and traits of men displaying the exercise-hypogonadal condition (see references 18 and 19 for further details).*

1) Low basal resting basal testosterone concentrations, are typically only 40-75% that of normal, healthy, age-matched sedentary men.
2) Low basal resting testosterone concentrations do not appear to be a short-term, transient phenomenon reflective of the acute stress and strain of exercise or sports training.
3) There appears to be either a dysfunction within the hypothalamic-pituitary-testicular regulatory axis, or an adjustment within this axis causing the new lower set-point for circulating testosterone.
4) A history of early involvement in organized endurance sport and exercise training, resulting in many years of almost daily exposure to high volumes of physical activity.
5) The type of sports training history most frequently seen in these men is prolonged, endurance exercise activities such as: marathon distance running, cycling, race walking, and triathlon training.

The other major androgenic-anabolic actions of testosterone do not appear to be detrimentally affected in exercise-hypogonadal men. For instance, there is no experimental evidence of decreased protein synthesis and, or muscle-mass development problems in exercise-hypogonadal men. Conversely, Izquierdo et al. has speculated that endurance exercise training (within exercise-hypogonadal men) may interfere with muscular power development due to the impairment of the anabolic hormonal status (25). Furthermore, Ratamess et al. have shown androgen receptor content is reduced after acute exercise, and this effect appears more robust with more stressful exercise (93). As noted earlier, exercise-hypogonadal men typically subject themselves to highly stressful exercise training bouts on a regular basis (16, 19).

Contrary to the above discussion, there could be beneficial physiological effects from the lowered testosterone associated with the condition. For example, some researches indicate that lowering testosterone may have cardiovascular protective effects and add to the decreased risk of coronary heart disease found in exercise-trained men (94). Scientists in Germany have provided strong direct evidence supporting this claim (95). The research by these investigators demonstrated that pharmacologically-induced reduction in endogenous testosterone concentrations results in significant increases in HDL in men. Whether the lowering of testosterone in exercise-hypogonadal men produces the same cardiovascular protective effect remains to be determined; but, most certainly, it represents an interesting future research issue to be addressed.

SUMMARY AND CONCLUSIONS

Over the last 25 years an increasing number of investigative research studies in men indicate endurance exercise training has significant effects upon the major male reproductive hormone, testosterone, and the hypothalamic-pituitary-testicular axis that regulates its production. Findings point to basal, resting-state testosterone (free and total concentrations) being significantly and persistently reduced in men involved in chronic endurance exercise training. That is, men with this condition exhibit an exercise-hypogonadism. The exact physiological mechanism inducing the reduction of testosterone is currently unclear, but is postulated to be a dysfunction within the hypothalamic-pituitary-testicular regulatory axis. This effect on the axis may also perhaps reflect a lowering of the set-point (i.e., readjustment) of the axis for what is deemed a more appropriate minimal amount of circulating testosterone for proper physiological function in exercise trained men (96-98). The time course for the development of the exercise-hypogonadal condition or the threshold of exercise training necessary to induce the condition remains unresolved and much further scientific investigative work is necessary to address these latter points. Table 1 provides a brief summarization of the major characteristics and traits commonly seen in men with the exercise-hypogonadal male condition (18).

The possibility exists for the reduced testosterone of exercise-hypogonadal men to disrupt some key anabolic or androgenic testosterone-dependent physiological processes and have adverse health consequences. To date only a very limited number of studies have addressed whether such processes are affected, and thus far the findings are somewhat inconclusive on this issue. Conversely, the alterations in testosterone concentrations brought about by endurance exercise training could have cardiovascular protective effects and thus be beneficial to the health of these men.

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