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Leptin: A Link Between Energy Imbalance and Exercise-Induced Amenorrhea in Female Athletes

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## Introduction

Between 5 to 25% of female athletes experience exercise-induced amenorrhea, depending on their sport and level of competition (2). The etiology of exercise-induced amenorrhea can be traced to the hypothalamus, where normal pulsatile secretion of GnRH appears to be inhibited, as reflected by low levels of FSH and particularly LH. Athletes with exercise-induced amenorrhea frequently exhibit low levels of leptin, as well as hypoglycemia, hypoinsulinemia, hypercortisolemia, hypothyroidemia, and a reduced basal metabolism (3). These are typical markers of energy-deficient state, in which hormones of the reproductive axis are inhibited and cortisol and other corticoids are elevated (5).

There is growing evidence that the hypothalamic amenorrhea seen in female athletes is due to a negative energy balance - specifically, inadequate energy intake for these women's high activity levels (3). Both amenorrheic and menstruating athletes tend to take in less dietary energy than is appropriate for their high levels of physical activity (2). In healthy, active women, disruption of LH pulsatility is seen when energy availability (the difference between dietary intake and energy expenditure) dips below a critical value of 20-25 kcal per day per kg LBM (3). One study which looked at the energy availability of menstruating versus amenorrheic elite athletes found that the amenorrheic athletes had only 50% of the energy availability of their menstruating peers (16 kcal per day per kg LBM versus 30 kcal per day per kg LBM) (3). Thus, these athletes are clearly in a state of energy deficiency. While the majority may not be significantly underweight, they typically display some weight loss and dieting behaviors and have low body fat and body mass index (2). Some may have lost significant weight while training and may display eating disorder symptoms, including obsessive dieting, a strict lowfat diet and avoidance of red meat and high-sugar foods (2). The combination of inadequate dietary intake, amenorrhea, and the subsequent bone density losses seen in these athletes comprise a constellation of symptoms known as the Female Athlete Triad (2).

## The Connection Between Energy Imbalance and Exercise-Induced Amenorrhea: Leptin

Leptin has been suggested as a link between amenorrheic athletes' energy status and reproductive dysfunction. The earliest work done on leptin, a hormone secreted predominantly by white adipose tissue, identified it as a "satiety factor" that, when injected into leptin deficient or normal mice, resulted in a marked reduction in food intake, body weight, and body fat. It was hypothesized that rises in circulating leptin levels served to prevent obesity by acting on higher centers in the brain which, in turn, decreased appetite and increased thermogenesis (1). This model was supported by the fact that leptin turned out to be the product of the obese (ob) gene in mice; mice who had recessive mutations in the ob gene developed hyperphagia, decreased energy expenditure, and early onset obesity (1). However, the promise of leptin as an "anti-obesity" treatment was diminished by evidence that high levels of endogenous leptin in humans did not prevent obesity - indeed, obesity is typically seen in conjunction with hyperleptinemia and has been postulated to be a result of leptin insensitivity (1).

As research on leptin continued, a more complex picture of the hormone's role in energy balance emerged. Currently, leptin expression is believed to be a key metabolic mediator which may "translate" nutritional information about the body's energy stores into neuroendocrine responses (5). Leptin plasma levels correlate directly with total body fat stores, increase after several days of overfeeding in humans, and begin falling within hours of initiation of fasting (1). These changes in leptin concentration appear to be regulated primarily by insulin but also by cortisol and reproductive hormones (2). Because leptin levels do not increase in response to a specific meal, it is unlikely that the hormone functions as a meal-related "satiety factor." Instead, it acts predominantly on hypothalamic centers to modulate more long-term responses to the body's energy status, including reproductive ones. Leptin's role as a "bridge" between energy balance and the reproductive axis has made it the subject of research in the causes of exercise-induced amenorrhea in female athletes.

Leptin levels are lower in female athletes than in sedentary females, and lower still in athletes with exercise-induced amenorrhea (5). Although leptin secretion is proportional to the amount of adipose tissue, and although female athletes tend to have a lower percentage of this tissue than sedentary women, the low levels of leptin in these athletes cannot be completely explained by their low body fat percentages alone (5). Instead, other factors beyond simply an increased lean mass appear to modulate the decline in leptin in both cyclic and amenorrheic athletes. These factors may be neuroendocrine responses to an energy deficit state, such as the presence of hypoinsulinemia and hypercortisolemia, both of which have been observed to decrease leptin levels (5, 9). Significantly, similar responses are also seen in amenorrheic, ostensibly "healthy", non-athletic women who engage in eating-disordered behaviors; despite their apparent normal weight and body fat percentages, these women display many signs of an energy deficit, notably low levels of thyroid hormone and leptin (7,8). Interestingly, this energy deficit appears to be due to restrictive eating patterns, including severe fat restriction (9), rather than actual caloric deficits (7).

In the case of exercise-induced amenorrhea, another important issue is whether athletes' low leptin levels - and subsequent amenorrhea - is due to a low food intake or to the stresses of athletic training. In other words, which is the more important component in the energy imbalance equation: the increased energy expenditure of exercise or the decreased energy intake of their diets? There appears to be no clear consensus on this point. One study that looked at leptin levels in healthy cyclical women who were either placed on low-calorie diet or subjected to an intense exercise regime concluded that intense exercise itself has no inhibitory effect on leptin, assuming that the athlete is consuming enough calories to compensate for her increased energy expenditure (4). In contrast, another study noted lower leptin levels in previously sedentary women who began an exercise program (8). Other studies have noted low leptin levels in both cyclical and amenorrheic athletes, with the levels of leptin typically being lower in the amenorrheic group (5). In primate studies, nutritional deficits, rather than stress, have been shown to be a more potent suppressor of the reproductive axis (7).

Regardless of the exact nature of the energy imbalance that results in decreased leptin, it is clear that, once levels of the hormone have fallen, the reproductive axis is affected. Study after study has demonstrated leptin's close ties with the reproductive axis. In healthy cyclic women, normal levels of leptin are thought to signal the readiness of the body's energy stores for reproduction (3). and a rise in leptin at adolescence may be a permissive signal for the onset of puberty (6). Indeed, leptin replenishment has been found to reverse the inhibitory reproductive effects of low food intake in primates (2). and restore ovulation in these animals (8). As well, administration of leptin antiserum suppresses LH pulsatility in rats; this pulsatility is restored when leptin is administered (4).

### Complicating the Picture: Glucose, Insulin, Thyroid Hormone, Cortisol, and Sex Hormones

In addition to low leptin levels, athletes with exercise-induced amenorrhea frequently have disturbances in glucose, insulin, thyroid hormone, and cortisol levels, as well as the expected declines in sex hormones. Current research is directed at untangling the interrelationships between these different hormones and proposing how they might work together to cause reproductive dysfunction in amenorrheic athletes. While the predominant regulator of leptin secretion is adiposity, acute changes in energy balance have been shown to disproportionately down- or up-regulate its levels in the blood (3). Thus, the negative energy balance seen in amenorrheic athletes may trigger a mechanism that suppresses leptin synthesis and secretion. This mechanism may be modulated by insulin, which is known to induce leptin secretion and is typically quite low in amenorrheic athletes (3). Multiple studies have found that insulin plays a central role in both the daily and long-term shifts in leptin levels (5).

Not surprising given its close relationship with insulin, glucose may also play a role in modulating leptin's actions. Several studies have suggested that it is glucose availability that specifically impacts LH pulsatility (3). Fluctuations in glucose availability, for example, are believed to act as a crucial metabolic signal which regulates GnRH secretion. These findings have led to a model of leptin in which its actions on reproduction are achieved by altering the body's glucose availability (3). It has been demonstrated, for example, that leptin levels fall in proportion to reductions in dietary carbohydrate (4).

Many amenorrheic athletes also exhibit hypothyroidemia, and indeed, leptin levels appear to be directly related to the level of circulating T3 thyroid hormone (the relationship between leptin and circulating T4 is not independent of body fat) (3). It is believed that the parallel declines in leptin and T3 levels in these women may act in tandem to decrease BMR and initiate the metabolic response to an energy-deficient state (7). This response may include an inhibition of the energy-costly reproductive axis (3).

How, exactly, leptin acts on the reproductive axis to produce amenorrhea is not yet fully understood. Some studies have reported that leptin enters the brain to stimulate GnRH neurons directly (4). while others report that, although leptin stimulates the secretion of

GnRH in vitro, GnRH neurons do not have detectable levels of leptin receptors and thus the stimulatory effect may not be directly mediated by leptin (1). This piece of data fits with the hypothesis that glucose, not leptin, directly affects GnRH secretion. On the other hand, leptin appears to directly stimulate gonadotropin release in ovarian follicular cells (1). Reports on the relationship between leptin and estrogen are equally confusing.. Some studies suggest that leptin does, indeed, have a regulatory role in estrogen production (1). while others found that neither oral contraceptives, hormone replacement therapy, nor estrogen administration had any effect on leptin levels (3). Interestingly, human ovaries express functional leptin receptors, and adipose tissue expresses estrogen receptors, suggesting a direct interplay between the two (3).

#### Conclusion: A Model for Leptin's Role in Exercise-Induced Amenorrhea

Can all these studies be brought together? How, ultimately, do lower leptin levels result in amenorrhea in athletes experiencing an energy imbalance? In an attempt to begin to explain the complex data on leptin's role in the hormonal abnormalities of amenorrheic athletes, Thong et al have proposed a model in which energy deficiency in these athletes results in low glucose levels. These low glucose levels, in turn, cause insulin levels to fall, a signal of energy deficiency that is then detected by adipose tissues. These tissues then down-regulate leptin synthesis and secretion. This down-regulated leptin, in conjunction with decreased levels of circulating T3, coordinate the myriad of neuroendocrine responses seen in these athletes. The energy-costing reproductive axis is shut down, while the beneficial adrenal axis is activated (3). The increasing levels of cortisol and other corticoid hormones may directly inhibit leptin, as well as inhibiting the generation of GnRH pulses (5).

In this model, low glucose levels represent the trigger for a chain of neuroendocrine events that result in decreased levels of leptin and an ultimate inhibition of LH pulsatility, leading to amenorrhea. However, although satisfying, this model is not entirely consistent with the body of clinical literature on amenorrheic athletes, as well as on anorexia nervosa patients and women with non-exercise-induced hypothalamic amenorrhea (4). As with so much of the research on endocrine issues, it is difficult to isolate out the role of any one hormone in the myriad of interactions and feedback loops that characterize leptin's role as a mediator between energy status and reproductive function. However, the identification of leptin as a critical intermediary in the path from energy deficiency to amenorrhea seen in female athletes represents an important step in enabling us to better understand the relationships between energy balance, metabolism, and reproduction.

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