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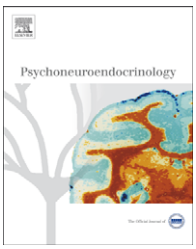

Physical activity and cortisol in Anorexia Nervosa

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Summary
Elevated physical activity is commonly observed among patients with Anorexia Nervosa (AN) and can manifest in several forms. While elevated physical activity may play a key role in the pathophysiology of this disorder, much remains unknown about it, including the relationship among its various manifestations, and their underlying mechanism(s). The purposes of the current study were to (1) quantify locomotor activity in inpatients with AN using an accelerometer, (2) determine the association between locomotor activity and exercise history and (3) determine the association between urinary cortisol and physical activity. Thirty-six women hospitalized with AN wore activity armbands for 48 h during the first 2 weeks of hospitalization, collected 24-h urine to measure cortisol, and completed rating forms. Activity counts varied more than four-fold among individuals but were consistent within individuals over the 2 monitoring days ($p<0.001$). Averaged 24-h activity counts were positively correlated with pre-hospitalization attitude towards exercise as measured by the Commitment to Exercise Scale (CES; $p=0.032$). Forty-two percent of women reported "high" exercise in the 3 months before hospitalization; compared to non-high-exercising patients, these women demonstrated a higher CES score ($p<0.001$) and a trend toward greater activity counts ($p=0.059$). Urinary cortisol was positively associated with activity counts ($p=0.044$) and CES score ($p=0.018$). These data suggest that some women with AN have a higher "drive" for physical activity that persists into early hospitalization. HPA axis abnormalities may be associated with this state.

1. Introduction

Anorexia Nervosa (AN) affects some 0.5–1% of young women in Western cultures and ranks among the most lethal of psychiatric disorders. Mechanisms maintaining this disorder remain poorly understood, and many patients remain chronically ill despite best available treatment (Walsh and Devlin, 1998).

Excessive physical activity is commonly observed among patients with AN, to the extent that it is considered by some to be a hallmark feature of the disorder (Casper, 1998; Kron et al., 1978). Over-activity may take the form of an increase in organized exercise routines, such as running and gym

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activities, as well as more diffuse activity, including pacing and fidgeting behavior. Such activity is assumed to facilitate weight loss in AN and has been linked in some (Kaye et al., 1988) (though not all (Birmingham et al., 2005)) studies to greater caloric requirements during the weight gain phase of treatment. Excessive exercise may be associated with a higher risk of osteopenia and stress fractures (LaBan et al., 1995), and has been associated with poorer outcome following hospitalization for the treatment of AN (Carter et al., 2004; Strober et al., 1997). Furthermore, it has been suggested that increased physical activity plays an etiologic role in development of AN in some patients (Davis et al., 1997; Epling and Pierce, 1991).

Despite its importance, much remains unknown about physical activity in AN. For example, it appears that activity levels are not universally elevated among patients with AN, but estimates vary widely as to the prevalence of this phenomenon (Hebebrand et al., 2003). One factor that may limit the study of physical activity in AN is the difficulty of delineating it, in part due to the various manifestations it may take (Hebebrand et al., 2003). A survey of existing literature reveals terminology including "excessive exercise" (Davis et al., 1993; Favaro et al., 2000), "compulsive exercise" (Brewerton et al., 1995); and "dependence" on exercise (Klein et al., 2004), each with slightly differing criteria, and most including both behavioral and psychological features. It is unknown whether these phenomena are related to each other, or to the apparent increase in more diffuse activity that has been labeled "hyperactivity" (Holtkamp et al., 2004) and "over-activity" (Casper, 1998). Furthermore, most studies rely on self-report or subjective measures. Few studies have attempted to quantify physical activity levels objectively, and the majority of these employed devices such as pedometers that provide data of limited sensitivity and time resolution compared with more recently available devices such as accelerometers. Finally, the biological underpinnings of elevated activity in AN have yet to be determined; while some provocative recent data link altered leptin levels to elevated activity, exercise, and/or restlessness in patients with AN (Hebebrand et al., 2003; Holtkamp et al., 2003), a number of other potential mediators may also play a role (Casper, 2006). Improved understanding of the interrelationship among various manifestations of physical activity in AN and of its associated pathophysiology could lend critical insight into new treatments for this often-refractory disorder.

AN is associated with numerous physiological disturbances, many of which are presumably related to the starved state, and some of which could potentially contribute to the persistence of the behavioral abnormalities characteristic of AN (Walsh and Devlin, 1998). As reviewed by Casper (2006), several of these, including alterations in thyroid, catecholaminergic, and HPA axis function, among others, might predispose patients to an elevated "drive" for physical activity. However, given that physical activity does not appear to be elevated in all patients with AN at all times (Hebebrand et al., 2003), it would seem fruitful to examine whether gradations in physiological abnormalities can be measured among patients depending on their level of activity (Favaro et al., 2000; Holtkamp et al., 2003, 2006). One disturbance characteristic of AN that has not, to our knowledge, been assessed with regard to exercise behavior and locomotor activity is that of hyperactivity of the HPA axis. As outlined below, several lines of evidence support further investigation of this possible link.

Cortisol, the primary end-hormone of the HPA axis, is elevated among underweight patients with AN, in association with increased central CRH and normal circulating levels of ACTH (Licinio et al., 1996). This is generally assumed to be a function of starvation, which is known to produce hypercortisolism. However, elevated cortisol may also be related to exercise behavior, which is also known to activate the HPA axis, independently of an eating disorder (Mastorakos et al., 2005). The animal model of "semi-starvation-induced hyperactivity" (also labeled "activity anorexia") provides further support for the role of excessive physical activity in exacerbating HPA axis abnormalities in patients with AN. In this paradigm, rodents are provided simultaneously with limited food supply and free access to a running wheel, which leads, paradoxically, to marked increases in wheel-running behavior and progressively inadequate food intake with starvation. This state has been associated with elevated levels of corticosterone, the rodent analog of cortisol (Burden et al., 1993); comparison between semistarved running rats and semistarved sedentary rats has shown a synergistic effect of starvation and hyperactivity on corticosterone (Broocks et al., 1990). Thus, it is possible that patients with AN who engage in high exercise exhibit greater elevations in cortisol than their less-active counterparts with the same degree of starvation.

Effects of HPA axis over-activity could in turn include subjective restlessness and motor agitation in AN (Casper, 2006). Evidence for this is provided by animal studies, in which administration of corticotropin releasing factor (CRF, which in turn stimulates release of corticosterone) leads to behavioral activation with increased locomotor activity (Sutton et al., 1982). Intriguingly, a comparison of rat strains differing in their HPA axis activity and reactivity showed varying vulnerability to the food restriction-induced hyperactivity syndrome described above, with higher HPA axis activation co-occurring with higher wheel-running behavior in food-restricted rats; these authors speculated that corticosterone in particular mediates the link between food restriction-induced weight loss and increased exercise (Duclos et al., 2005). Most compellingly, administration of a CRF antagonist attenuates or prevents the development of exercise-induced anorexia (Kawaguchi et al., 2005; Rivest and Richard, 1990), further supporting a causal role of HPA axis disturbance in behavioral hyperactivity. Thus, it is plausible that some element of HPA axis over-activation (e.g., increased production of CRH and/or cortisol) serves to mutually reinforce excessive physical activity observed in some patients with AN. This hypothesis remains untested in people.

The purposes of the current study were three-fold: first, we aimed to quantify locomotor activity in a population of inpatients with AN during early hospitalization using an accelerometer and to determine the psychological and behavioral correlates of this activity. Second, we aimed to measure the proportion of patients endorsing criteria for "high" exercise prior to hospitalization, and the clinical features, including inpatient locomotor activity, associated