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Physiological and psychological effects of testosterone during severe energy deficit and recovery: A study protocol for a randomized, placebo-controlled trial for Optimizing Performance for Soldiers (OPS)

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ABSTRACT

Background: The physiological consequences of severe energy deficit include hypogonadism and the loss of fat-free mass. Prolonged energy deficit also impacts physical performance, mood, attentiveness, and decision-making capabilities. This study will determine whether maintaining a eugonadal state during severe, sustained energy deficit attenuates physiological decrements and maintains mental performance. This study will also assess the effects of normalizing testosterone levels during severe energy deficit and recovery on gut health and appetite regulation.

Methods: Fifty physically active men will participate in a 3-phase, randomized, placebo-controlled study. After completing a 14-d, energy-adequate, diet acclimation phase (protein: 1.6 $g \cdot kg^{-1} \cdot d^{-1}$; fat: 30% total energy intake), participants will be randomized to undergo a 28-d, 55% energy deficit phase with (DEF + TEST: 200 mg testosterone enanthate per week) or without (DEF) exogenous testosterone. Diet and physical activity will be rigorously controlled. Recovery from the energy deficit (ad libitum diet, no testosterone) will be assessed until body mass has been recovered within ± 2.5% of initial body mass. Body composition, stable isotope methodologies, proteomics, muscle biopsies, whole-room calorimetry, molecular biology, activity/sleep monitoring, personality and cognitive function assessments, functional MRI, and comprehensive biochemistries will be used to assess physiological and psychological responses to energy restriction and recovery feeding while volunteers are in an expected hypogonadal versus eugonadal state.

Discussion: The Optimizing Performance for Soldiers (OPS) study aims to determine whether preventing hypogonadism will mitigate declines in physical and mental function that typically occur during prolonged energy deficit, and the efficacy of testosterone replacement on recovery from severe underfeeding.

Trial Registration: NCT02734238.

1. Introduction

Strenuous work and inadequate energy intake during military operations produce severe energy deficits, deplete body energy stores, result in fat-free mass (FFM) loss, degrade performance, and increase risk of injury [1–5]. The FFM loss induced by military operations is

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modifiable, as higher-protein diets [$> 0.8\ g \cdot kg^{-1} \cdot d^{-1}$ and within the Acceptable Macronutrient Distribution Range for protein (10–35% total energy intake)] have consistently been shown to spare FFM and preserve muscle anabolic sensitivity in situations where the energy deficit is ~40% of total daily energy expenditure (TDEE) [6–8]. However, under conditions of severe (~50–60% of TDEE) energy deficit, higher-protein diets fail to augment FFM retention [9,10]. Decrements in total body mass and FFM in men generally occur when circulating levels of testosterone are substantially reduced [11].

The reductions in testosterone that occur during severe energy deficit may diminish the efficacy of increasing protein intake to spare FFM. In healthy young males, the suppression of endogenous testosterone production has myriad adverse physiological consequences including reduced FFM, increased adiposity, and decreased muscle strength [12–15]. Finkelstein et al. [13] recently demonstrated that decreased testosterone levels (from 530 to 350 ng·dL-1), achieved by goserelin acetate administration to reduce endogenous testosterone and estradiol production, result in increased adiposity, and further reductions to ≤ 200 ng·dL-1 are accompanied by skeletal muscle atrophy and decreased muscle strength. Importantly, testosterone decreases of this magnitude occur during military training and sustained operations, and are associated with concomitant decreases in FFM [11,16–19]. Although dietary macronutrient manipulations have proven unsuccessful at mitigating the endocrine response to severe negative energy balance [20], pharmacologic interventions that restore anabolic hormone concentrations to normal levels have been shown to promote nitrogen retention despite energy deficit [21–23]. Whether preventing declines in testosterone during conditions simulating severe, sustained energy deficit enhances the FFM-sparing effects of a higher-protein diet has not been studied.

The potential influence of testosterone maintenance on physiological and body composition recovery from severe energy deficit remains unclear. In general, refeeding following energy deficit is marked by the preferential accumulation of adipose tissue and not FFM, a phenomenon known as “rebound fatness” [18]. It is possible that the loss of body fat during energy deficit elicits a persistent suppression of metabolic rate during recovery, whereas the reductions in FFM promote hyperphagia in recovery from energy deficit [24]. Thus, we suspect that if testosterone levels are maintained during severe energy deficit, FFM will be spared, reducing subsequent hyperphagia and relative fat mass gain during refeeding and thereby setting the conditions for a more favorable recovery.

1.1. Effects of testosterone on personality, mood, and cognition during energy deficit

Testosterone has the potential to augment cognitive performance [25–29], mood [30–34], assertiveness [35,36], and risk-taking [37–39]. A growing body of neuroimaging studies has suggested that testosterone may exert these effects by modifying the functioning of specific brain regions, including the amygdala and orbitofrontal cortex, that control emotion processing, self-restraint, and evaluation of threat [40–47]. Testosterone administration during a period of sustained energy deficit may reduce the adverse effects on mood associated with low testosterone levels. Furthermore, the effect of testosterone supplementation on sleep quantity and quality has not been examined, but there may be a relationship between endogenous testosterone levels and both sleep duration and length of wakefulness [48–50].

1.2. Effects of testosterone on appetite regulation during energy deficit

Appetite-mediating hormones, including peptide-tyrosine tyrosine (PYY), glucagon-like peptide-1 (GLP-1), and ghrelin contribute to the motivation to eat and hunger after weight loss and may underlie the common tendency for weight regain [51]. However, supporting evidence is predominantly derived from studies in obese populations. Given the high prevalence of dieting for weight loss and body weight cycling in non-obese populations (e.g., adolescents/adults with body image concerns, athletes of weight sensitive competitive sports, and military personnel required to meet body weight standards) and the increased risk of obesity that accompanies these behaviors [52], improving current understanding of adaptive responses of appetite-mediating hormones to weight management in non-obese populations is imperative.

1.3. Effects of testosterone on gut microbiome and intestinal permeability during energy deficit

Disruption or dysfunction of the gastrointestinal barrier can increase intestinal permeability, causing translocation of bacteria and their pro-inflammatory components [e.g., lipopolysaccharide] into systemic circulation [53]. The resulting low-grade systemic inflammation increases susceptibility to acute and chronic disease [54], increases risk for nutrient deficiency [55], adversely impacts cognitive and physical performance [53], and exacerbates gastrointestinal barrier dysfunction [56]. Evidence suggests testosterone may mediate intestinal permeability [57,58] and conversely, the gut microbiome may modulate testosterone levels [59].

1.4. Objectives, design and methods

1.4.1. Primary study objectives

I. Determine the extent to which maintenance of a eugonadal state by exogenous testosterone administration attenuates the effects of severe, sustained energy deficit on body composition (body mass, FFM and fat mass), skeletal muscle (mass, strength/power/endurance, proteomics, intramuscular regulators of metabolism, protein synthesis and proteolysis), metabolism (energy expenditure, substrate oxidation and nitrogen balance) and physiological status (androgens, stress and metabolic hormones, inflammation, biomarkers of nutritional status, circulating and intramuscular substrates and blood lipids).
II. Determine the effects of exogenous testosterone administration during severe, sustained energy deficit on subsequent recovery of body composition, skeletal muscle, and metabolic and physiological status.

1.4.2. Secondary study objective

III. Determine the effects of severe, sustained energy deficit and associated hypogonadism on mental fatigue and other aspects of mood, cognitive performance, brain function and sleep.
IV. Determine the extent to which the detrimental effects of sustained energy deficit on mood, cognitive performance, and sleep are attenuated by pharmacological testosterone treatment.

1.4.3. Tertiary study objectives

V. Determine the effect of testosterone maintenance on appetite and adaptive responses of appetite-mediating hormones during energy deficit and body mass recovery in non-obese adults.
VI. Determine the effects of energy deficit with and without testosterone treatment on gut microbiota composition, function, and activity.
VII. Identify associations between gut microbiota composition and function, host energy/substrate metabolism, body mass change, and the composition of body mass loss and regain.

1.5. Institutional review board approval and trial registration

The study protocol was approved by the Institutional Review Board