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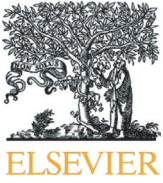
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Commentary

Testosterone replacement for male military personnel – A potential countermeasure to reduce injury and improve performance under extreme conditions


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Tactical operators, inclusive of soldiers in the military, are reliant upon their physiological and psychological state in often volatile and extreme life or death situations that require correct decisions and precise actions to ensure operational success with minimal collateral damage. Accordingly, the development of physical and mental resilience are hallmarks of prophylactic and remedial programs designed to ensure military personnel are combat ready, thus optimising their capacity to perform at expert levels, while reducing their risk of injury or the severity of injury sustained. Unfortunately, despite best efforts, current practices have not overcome the significant logistical challenges confronting a military service member's routine exposure to moderate and severe energy deficits upon deployment, resulting from unyielding energy demands and restricted energy intake during missions [1]. Consequently, these episodes of semi-starvation under complex and extreme tactical environments produces a cascade of interlinked negative outcomes, including a hypogonadal endocrine state (suppressed testosterone production), loss of muscle-bone mass and strength, reduced functional capacity, compromised cognition, and a suppressed immune system, culminating in greater susceptibility to injury, illness and sub-optimal performance, jeopardising their own welfare and the welfare of their comrades.

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Normal physiologic levels of serum testosterone expressed in young men in the United States ranges from 10.4 to 34.7 nmol/L (300 to 1000 ng/dL) [2]. However, military personnel express up to 65% less serum testosterone as a consequence of stress and duress applied in military training [3], reflecting the inevitable response also experienced by deployed military soldiers. To remedy hypogonadal states induced by moderate-to-severe energy deficits and extreme operational conditions, exogenous testosterone supplementation (testosterone replacement therapy) is a viable countermeasure to effectively reverse the cascade of physical and mental consequences experienced by tactical operators [4]. In alignment with clinical treatment of men with chronically low testosterone levels, the updated *Endocrine Society* clinical practice guidelines recommend a wide array of pharmacotherapies, the most prominent of which is testosterone enanthate; an easily administered synthetic derivative of testosterone through intramuscular injection; to be given at a starting rate of 75–100 mg/week on average [2]. Such strategies in the hypogonadal civilian have been shown to produce predictable yet important benefits, such as increased myogenesis and osteogenesis (muscle-bone mass and strength), improved physical function, reduced anxiety, increased mood, and increased cognition (i.e. attention, visual scanning ability, executive function and psychomotor speed) [5,6]. These qualities are critical to the performance of military personnel, though whether testosterone replacement produces equivalent outcomes under moderate-to-severe energy deficits as a consequence of extreme operational conditions has yet to be clarified.

In *EBioMedicine*, Pasiakos and colleagues [1] report their initial results from an impressive three-phase, proof-of-concept, randomised, double-blind, placebo-controlled trial; the first known rigorously controlled study exploring this critical research question. We commend the Military Nutrition Division of the US Army Research Institute of Environmental Medicine and the Pennington Biomedical Research Center for their ambitious undertaking to pursue this line of inquiry. Using a 14-day eucaloric control period, 28-day intervention of 200 mg/week testosterone enanthate supplementation with an exercise- and diet-induced energy deficit, and subsequent 14-day ad-libitum recovery period; this study demonstrated a reduction in weight loss and

improvement in lean mass gain, producing benefits in body composition and health status. However, the enduring effect of testosterone enanthate has yet to be realised in their cohort, owing to the short-term nature and time-points utilised, which may partly explain the limited bandwidth of positive benefits described. For example, strength benefits when supplementing with testosterone enanthate are typically observed after 6 weeks of administration [7] with ergogenic muscle mass increases preceding strength benefits. This may partly explain the observed increase in muscle mass but not strength in Pasiakos and colleagues [1], assessed after only 28 days of treatment. In addition, the single-joint isokinetic muscle function test used in their trial is limited by mechanical specificity relative to training and operations of military personnel, thus may lack sensitivity. The absence of muscle function improvement in their trial must be considered in this context.

Replica trials utilising longer-term interventions with longer-term follow-up would be the next logical step to interrogate the therapeutic utility of this treatment method for this population. This is vital as the anabolic effects of testosterone replacement therapy in military personnel has long-term implications [8], including protective effects on muscle and bone (which may prevent stress fractures or load carriage incidents [5]), and the likely improvement in recovery from completed missions or injuries sustained. Most critical to the future of this work is the evident generation and accumulation of myonuclei during hypertrophy [8], as myonuclei do not experience apoptosis during atrophy or programmed cell death, thus new muscle mass developed during youth and through ergogenic means provides lasting physiological benefits that facilitates faster re-growth of lost muscle [9], faster re-gain of lost muscle strength, and faster recovery in unavoidable cases where atrophy has to occur. This also has considerable potential to delay the onset of sarcopenia and osteoporosis later in life; a downstream benefit worthy of exploration. Lastly, controversy surrounding the use of exogenous testosterone and aggressive prostate cancer risk in older age remains unresolved, as prostate cancer is known to thrive in testosterone rich environments. Fortunately, this does not appear to be supported in the literature, with increased exogenous or endogenous testosterone levels in young men not associated with increased risk of prostate cancer, increased prostate-specific antigen (PSA) levels or increased prostate cancer aggressiveness at diagnosis [10], which would otherwise present an ethical dilemma to this treatment pathway in military personnel.

Longer-term companion and observational studies are advised to directly examine many of the implicated and associated benefits and risks for male military personnel over the mid-to-long term. Furthermore, with the increased recruitment and integration of female personnel in to military combat positions, studies evaluating the female endocrine response to severe stress and its consequences are also needed.

Author contributions

NHH and RUN contributed equally to all components of the development and writing of this manuscript. Specifically, each author was involved in the conception, planning, preparation, drafting, revising and completion of the final manuscript.

Declaration of Competing Interest

NHH and RUN declare no conflicts of interest.

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