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Reversible male hypogonadotropic hypogonadism due to energy deficit

Short title: Energy deficit-associated hypogonadism

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Summary

Context: Calorie restriction and overtraining are increasingly seen in young men who suffer from increasing societal pressure to attain a perceived ideal male body image. The resulting energy deficit can lead to multiple endocrine consequences, including suppression of the male gonadal axis.

Design: We reviewed the literature, including two unpublished cases.

Results: We identified 23 cases, aged median (range) 20 years (16-33), with a body mass index of 15.9 kg/m^2 (12.5-20.5). Total testosterone was 3.0 nmol/L (0.6-21.3), and luteinizing hormone (LH) 1.2 mIU/L (<0.2-7.5), with 91% of cases demonstrating hypogonadotropic hypogonadism. Associated findings included evidence of growth hormone resistance (increased growth hormone in 57% and low insulin like growth factor-1 in 71%), hypercortisolaemia (50%), and a nonthyroidal illness picture (67%). In cases with longitudinal measurements following weight regain, serum testosterone (n=14) increased from median [interquartile range] 3.2 nmol/L [1.9-5.1] to 14.3 nmol/L [9.3-21.2] (p<0.001), and LH (n=8) from 1.2 IU/L [0.8-1.8] to 3.5 IU/L [3.3-4.3] (p=0.008).

Conclusions: Hypogonadotropic hypogonadism can occur in the context of energy deprivation in young otherwise healthy men and may be underrecognized. The evidence suggests that gonadal axis suppression and associated hormonal abnormalities represent an adaptive response to increased physiological stress and total body energy deficit. The pathophysiology likely involves hypothalamic suppression due to dysregulation of leptin, ghrelin and proinflammatory cytokines. The gonadal axis suppression is functional, because it can be reversible with weight gain. Treatment should focus on reversing the existing energy deficit to achieve a healthy body weight, including psychiatric input where required.

Introduction

Caloric restriction, especially if combined with excessive energy expenditure can result in a total body energy deficit with detrimental effects on multiple endocrine axes, in particular the reproductive axis [1]. Underlying the impetus to achieve a negative energy balance are body image disorders that have historically been recognised largely in women. The

combination of disordered eating/low energy availability, amenorrhoea, and reduced bone mineral density, has been officially recognised as the 'female athletic triad' in 1992 [2].

Recently, there has been a gradual shift of attention towards men and with it, the ever increasing need to pursue a fit muscular physique. Calorie restriction and overtraining can be seen in young men exposed to significant societal pressure to attain what is perceived to be the 'ideal' male body image. Muscle dysmorphia, characterised by a pathological preoccupation with muscularity, has been recognised in the Diagnostic and Statistical Manual of Mental Disorders 5th edition (DSM-5) as a subtype of the body dysmorphic disorder, and overlaps with eating disorders/anorexia [3]. The recognition that whole body energy deficits, commonly in the of context inadequate caloric intake combined with excessive exercise can lead to a number of serious adverse health outcomes, including significant endocrine complications in both men and women, has prompted the International Olympic Committee (IOC) to define this condition as 'relative energy deficit in sport' (RED-S) in 2014, identifying low energy availability as the key aetiological factor [4]. Although exercise-associated hypogonadism in men has been reported since the 1980s [5], RED-S remains underrecognized and overlooked in clinical practice in men. Endocrine consequences of energy deficit in men have not systematically reviewed before.

To identify clinical features and endocrine phenotypes associated with energy deficit in men, and to assess the response to weight regain, we summarise the existing literature. We also discuss the underlying pathophysiology.

The material discussed in this review is based on PubMed database searches using the search terms "testosterone", "androgen", "hypogonadism", "anorexia", "weight loss", "energy deficit", "exercise", and "men" from inception to December 2018.

Summary of published cases

Including two previously unpublished case reports from our institution (for case details, refer to supplementary material), we identified 23 post-pubertal case reports of energy deficit-associated hypogonadism (**Table 1**) [6-17]. All were young men, with a median age (range) 20 years (16-33), and were mostly underweight, with a median BMI of 15.9 kg/m^2 (12.5-20.5). Median total testosterone was 3.0 nmol/L (0.6-21.3), and LH 1.2 mIU/l (<0.2-7.5), with 91% of cases demonstrating (usually marked) hypogonadotropic hypogonadism

(defined as total testosterone below the reference range and a LH below the upper limit of the reference range). In addition, cases had evidence of GH resistance (increased GH in 57% and low IGF-1 in 71%), hypercortisolaemia (50%), and a nonthyroidal illness picture (low T3 in 67% with either low or normal T4 and TSH) (**Table 1**). In cases with longitudinal measurements following weight regain, serum testosterone (n=14) increased from median [interquartile range] 3.2 nmol/L [1.9-5.1] to 14.3 nmol/L [9.3-21.2] ($p<0.001$), and LH (n=8) from 1.2 IU/L [0.8-1.8] to 3.5 IU/L [3.3-4.3] ($p=0.008$) (**Figure 1**).

Male hypogonadotropic hypogonadism due to energy deficit

We identified 23 cases of -usually profound- hypogonadotrophic hypogonadism associated with energy depletion in relatively young, otherwise healthy young men [6-17] (supplementary material). While anecdotal, this evidence suggests that energy deficits leading to a low BMI can profoundly depress the male hypothalamic-pituitary-gonadal axis. The reversibility following weight regain in reported cases suggests that the hypogonadism is functional. Similar to what is reported in women [2,18], affected men had involvement of other endocrine axes, demonstrating elevated serum cortisol and evidence consistent with GH resistance and a euthyroid sick syndrome (**Table 1**).

<u>An underrecognized condition in men</u>

From an evolutionary perspective, hypogonadotropic hypogonadism associated with low energy availability can be considered a defence mechanism to prevent reproduction in adverse conditions. It is generally thought that women are more susceptible, due to the greater energy demands of pregnancy [18]. Starvation associated amenorrhea has been reported since antiquity, and the importance of easily mobilised energy from a minimum amount of body fat to maintain ovulatory function was well recognised in the 1970s [19]. The American College of Sports Medicine formalised the female athlete triad of disordered eating, amenorrhea and osteoporosis in 1992 [2]. However, the male-encompassing term RED-S was introduced by the IOC only in 2014 [4].

The underrecognition in men may in part due to the absence of specific hypogonadal features akin oligo/amenorrhoea in women, a situation analogous to the delayed recognition of prolactin excess. In addition, the fact that the male gonadal axis can be vulnerable to energy deprivation may be underappreciated. Moreover, although classical eating disorders such as anorexia nervosa have a female preponderance, estimates suggest that ~30% of

young people diagnosed according to the DSM-5 condition "Avoidant & Restrictive Food Intake Disorder" are men [20]. Still, the literature on male-specific consequences of energy deficit and associated endocrinopathies are largely limited to case reports and small case series [7-17] (**Table 1**).

While pure anorexia nervosa-like eating disorders occur in men, male body dysmorphia can be driven by the need to confirm to stereotypic 'masculinity' and to be fit rather than being thin [3,21]. Men who perceive their bodies as small and inadequately muscular often commit to rigorous training schedules resulting in disruption and negative consequences in both work and social life [3,21]. A pathological obsessive preoccupation with muscularity is the defining trait of muscle dysmorphia, a subcategory of body dysmorphic disorder. These individuals typically aim to drastically reduce their body fat percentage with calorie restriction, before redirecting their focus to building muscle bulk via demanding exercise regimes and consumption of large amounts of lean protein and commercial protein supplements, some of which may contain undeclared anabolic agents [3,21].

Many individuals lack the obsessive criteria necessary to formally diagnose muscle dysmorphia but participate in similar lifestyles and thus the prevalence of related hypogonadism is likely underestimated. Like in our case studies, men may simply unaware of the endocrinological consequences of the combination of calorie restriction and overtraining.

Differential diagnosis

From a clinical perspective, hypogonadotropic hypogonadism secondary to a negative energy balance is a diagnosis of exclusion. Congenital hypogonadotropic hypogonadism can generally be excluded due to evidence of normal pubertal development. A targeted work-up is necessary to exclude potential causes of acquired hypogonadotropic hypogonadism, e.g. hyperprolactinaemia, pituitary lesions, head trauma, haemochromatosis, or drugs (opioids, glucorticoids and anabolic steroids).

Anabolic steroid misuse, which may be covert, is an important differential to consider in young men with otherwise unexplained biochemical hypogonadotropic hypogonadism. While historically largely restricted to competitive athletes, increasing focus on male body image and easier access via internet sales has led to increasing use of anabolic steroids in

non-athletes to enhance physical appearance [22]. A recent meta-analyses has estimated a global lifetime prevalence rate for men of 6.4% [23]. Anabolic steroids suppress endogenous androgen production via negative feedback inhibition of gonadotrophin-releasing hormone (GnRH). As synthetic anabolic steroids usually do no cross react in testosterone assays, the biochemical picture is indistinguishable from severe functional hypogonadotropic hypogonadism due to energy deficit. While clinical presentations overlap, anabolic steroid users typically have a muscular physique with atrophic testes, and, due to high androgen exposure, lower SHBG, lower high-density lipoprotein (HDL), and higher haemoglobin levels [22]. In contrast, men with energy deficits typically have higher SHBG [24-26] and higher HDL, and, due to androgen deficiency, lower haemoglobin levels. While associated endocrine manifestations in non-reproductive tissues (e.g. euthyroid sick syndrome, hypercortisolaemia, evidence of GH resistance, discussed below) may favour a diagnosis of energy deficit rather than anabolic steroid misuse, ultimately, there is no diagnostic test (apart from asking the patient) that can distinguish hypogonadism caused by energy deficit from incomplete recovery following discontinuation of anabolic steroids. Men may not always disclose this information, and/or may be unknowingly exposed to undeclared anabolic steroids in dietary supplements.

In the case reports reviewed here [6-17] (supplementary material), features that favour the diagnosis of energy deficit-associated hypogonadism include the history of marked weight loss, low haemoglobin, increased SHBG, evidence of associated non-reproductive endocrine abnormalities, and the relatively rapid (within months) gonadal axis recovery with weight regain and reduced exercise (Table 1, Figure 1).

Pathophysiology

The male gonadal axis is sensitive to the effects of exercise-related stress especially if combined with concomitant calorie restriction. Cross-sectional studies have reported lower serum testosterone concentrations in male endurance athletes compared to non-active controls [5,27,28]. Longitudinal studies in men, especially in those engaging in ultra-endurance exercise, such as marathons and cross country cycling events have reported marked reductions of serum testosterone by up to 70% [29,30] .

In studies among healthy young volunteers participating in the 8-week US Army Ranger course, a gruelling exercise regimen combined with a restrictive diet (~2,200 calories per

day), body weight decreased by 8-12 kg, total testosterone by 70-80% and SHBG increased by 46-60% [24,26]. Gonadal axis recovery occurred within 6 weeks after completion of the course [26]. In healthy young men subjected to experimental caloric restriction (without concomitant exercise) for 3 weeks, body weight decreased by 6 kg and serum testosterone by 2.8 nmol/L, a decline reversible by refeeding [31]. In healthy men subjected to acute and prolonged (72 hour) fasting, serum testosterone decreased from 20.8 to 13.6 nmol/L, and SHBG increased by 20% [25].

Clinical studies in men suggest that energy deficit associated hypogonadism is, like in women, due to central suppression of the gonadal axis. In highly trained male marathon runners, compared to healthy controls, while there was no difference in serum testosterone and testicular response to human chorionic gonadotrophin (hCG), marathon runners had diminished frequency and lower amplitude of spontaneous LH pulses [32]. In addition, in aforementioned experimental caloric restriction study [25], 72 hour fasting decreased the typical LH pulsatility pattern observed in the fed state. In male rats, early studies demonstrated that while fasting reduces serum and testicular testosterone concentrations as well as circulating LH, testicular responses to hCG and pituitary responses to GnRH were not affected, suggesting a hypothalamic effect [33]. Indeed in subsequent male rat experiments, fasting-associated suppression of the gonadal axis were fully prevented by concomitant GnRH treatment [34].

Recent evidence suggests that KNDy (kisspeptin/neurokinin B/dynorphin) neurons in the arcuate nucleus of the mediobasal hypothalamus are major upstream regulators of GnRH neuron activity [35]. Infusion of kisspeptin has been demonstrated to increase LH pulsatility in women with hypothalamic amenorrhoea [36], and to increase LH pulse frequency and LH secretion in obese men with low testosterone [37], suggesting that both energy deficit and excess lead to central gonadal axis dysregulation by similar mechanisms.

Circulating leptin, a hormonal indicator of fat reserves, has been reported to be low in men with hypogonadotropic hypogonadism due to energy deficit, and in experimental settings, its replacement appears to reverse starvation-associated gonadal axis suppression. In healthy men, short term (72 hours) starvation leads to marked reductions in leptin levels out of proportion to the degree of fat mass loss, associated with blunted GnRH pulsatility and reductions in circulating testosterone [25]. In this experimental setting, replacement doses of

recombinant leptin administered during fasting prevented the starvation-associated gonadal axis suppression and maintained GnRH pulsatility, suggesting that leptin acts upstream of GnRH [25], potentially through stimulation of GnRH secretion via kisspeptin [35]. Similar evidence for efficacy of recombinant leptin in improving reproductive functions has also been reported in a controlled study of women with hypothalamic amenorrhea due to energy deficit. Interestingly in this study, leptin treatment also increased free triiodothyronine (T3), free thyroxine (T4), IGF-1 and bone remodelling markers, suggesting that adverse consequences of energy deficit-associated leptin deficiency may extend beyond the gonadal axis [38]. Obesity is associated with leptin resistance and supressed hypothalamic kisspeptin gene expression, and studies in obese men suggest that circulating leptin and testosterone interact in a self-perpetuating cycle promoting adiposity and reproductive dysfunction [39].

Ghrelin, an orexigenic peptide produced mainly by oxyntic cells in the stomach, has been postulated to play a role in the regulation of male gonadal axis. During periods of starvation and in healthy individuals immediately before a meal, elevated levels of ghrelin act to stimulate appetite and promote increased calorific intake. In experimental studies in healthy men, ghrelin treatment reduced LH concentrations and pulsatility, with an associated reduction in circulating testosterone [40]. Ghrelin also stimulates growth hormone (GH) and adrenocorticotropic hormone (ACTH) release [18], potentially contributing to other adaptive endocrine manifestation of male energy deficit (discussed below).

In clinical studies, energy deficits are associated with increases in circulating inflammatory cytokine such as interleukin (IL)-4, IL-6, IL-8, IL-10 and highly sensitive C-reactive protein (hs-CRP) [26,41]. Observational studies have also reported an inverse relationship of circulating pro-inflammatory cytokine and testosterone concentrations in community dwelling men [42]. In preclinical studies, cytokines have been reported to supress the male gonadal axis [43]. In addition, experimental low-dose IL-2 administration inhibits GnRH and/or LH secretion in older men [44]. Interestingly, increased pro-inflammatory cytokines are likewise postulated to contribute to gonadal axis suppression seen in obese men [39], again reinforcing the concept that both energy deficit and excess lead to central gonadal axis dysregulation by similar mechanisms.

While individual susceptibility likely varies (see below), the concept of body weight- or body fat- thresholds below which gonadal axis function is impacted in humans has largely

been explored in women. Prospective studies in amenorrhoeic women with anorexia nervosa undergoing nutritional rehabilitation have reported that achieving 90% of ideal body weight [45], or a minimum 17% to 19% body fat [19,46], is necessary for the resumption of menses. Evidence in men is very limited. One small longitudinal study in 5 men with anorexia evaluating LH responses to GnRH stimulation reported that while LH responses were blunted at body weights below 40kg, LH response normalised when a body weight of more than 50 kg was achieved [9].

The variables that influence the susceptibility to energy deficit-associated gonadal axis suppression are not well understood, but likely to be a multifactorial combination of genetic, hormonal and environmental factors. While differences in the severity and chronicity of the energy deficit, total amount of weight loss, as well as baseline weight may be important factors in influencing the degree of hormonal suppression and subsequent recovery, susceptibility may be governed by underlying genetic factors. Interestingly, rare sequence variants in genes involved in development of congenital GnRH deficiency, such as the Kallmann syndrome 1 sequence gene (*KAL1*) and the fibroblast growth factor receptor 1 gene (*FGFR1*), were found in 7 of 55 women with hypothalamic amenorrhea vs. none in 422 controls with normal menstrual cycles, suggesting that these variants may confer increased susceptibility to GnRH dysregulation seen in functional hypothalamic amenorrhoea [47].

Other endocrine consequences of energy deficit

In individuals with functional hypogonadotropic hypogonadism secondary to total body energy deficits, a number of other endocrine manifestations can also occur including evidence of GH resistance, hypercortisolaemia and nonthyroidal illness (**Table 2**).

The combination of confirmed elevated GH and low IGF-1 suggests acquired GH resistance. GH resistance in nutritionally deficient patients is supported by evidence of hepatic GH receptor downregulation, and, in adolescent girls, lack of IGF-1 response to supraphysiological infusions of recombinant human GH [48]. GH resistance however appears to be limited to GH effects that are IGF-1 mediated. For example, in women with anorexia nervosa, replacement-dose recombinant human IGF-1, but not supraphysiologic recombinant human GH treatment, increases markers of bone formation [18]. By contrast, direct (IGF-1 independent effects), e.g. on body composition are preserved. During times of

increased physiological stress and low-calorie intake, high levels of GH are considered an adaptive response to maintain euglycaemia via increased lipolysis, a mechanism which is independent of IGF-1 [18,48]. GH and IGF-1 levels usually return to normal following weight regain [18].

Cortisol levels are usually around twice the upper limit of normal in patients with low calorific intake and overtraining. High ghrelin levels during starvation stimulate ACTH release and subsequent hypercortisolaemia [18]. In men, hypercortisolaemia has been demonstrated to be mediated by increased glucocorticoid secretory burst mass, rather than increased burst frequency, duration or cortisol half-life [49]. Finally, increased physiological stress is typically associated with a reversible nonthyroidal illness picture [18].

While these endocrine adaptations are present to maintain euglycaemia, to decrease unnecessary energy expenditure, and to redirect vital energy reserves away from less important functions such as reproduction, the long term consequence of these endocrine adaptations are not known and may potentially be harmful. Male hypogonadism due to energy deficit can contribute to fatigue, sexual dysfunction, loss of muscle and bone mass and an increased risk of stress fractures [7-17].

Treatment

Given its functional nature, energy deficit-associated hypogonadism is reversible with weight regain (**Figure 1**), analogous to the reversibility of obesity-associated hypogonadism with weight loss [39]. Therefore, as recommended in women [18], treatment should focus on reversing the existing energy deficit by ensuring adequate nutrition, achievement of a healthy body weight, and avoidance of excessive exercise. In men with established body dysmorphic disorders, psychiatric input is required. Whether testosterone treatment has clinical benefits in men with energy deficit-associated hypogonadotropic hypogonadism is not known. More evidence is required to guide if and when testosterone treatment should be considered.'

Conclusions

Caloric restriction and overtraining may be increasing in young men who strive to attain the 'ideal' male physique. This combination can result in detrimental effects on the gonadal axis, a complication that may be underrecognized and underappreciated in clinical practice.

This case series and review demonstrates the sensitivity of the male reproductive axis to energy deprivation and highlights the importance of early detection and targeted management. Recovery with weight gain suggests that the gonadal axis suppression is functional and reversible, and therapy should focus on weight regain to achieve, and maintain, an appropriate body weight.

Figure Legend

Figure 1. Circulating biochemical gonadal axis parameters before and after weight gain.

Shown are paired serum total testosterone (n=14 cases) (A) and LH (N=8 cases) (B) concentrations before and after weight gain. Box plots demonstrate the median (horizontal lines), interquartile range (boxes) and range (vertical lines). Outliers are represented by dots. Changes in biochemical parameters after weight gain were analysed by means of nonparametric Wilcoxon signed rank test.

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Table 1. Summary of case reports of energy deficit-associated male hypogonadism

Characteristic	Median	Range	N	% Outside reference range
Age (years)	20	16-33	18	
BMI (kg/m^2)	15.9	12.5-20.5	18	89
T (nmol/L)	3.0	0.6-21.3	23	96
LH (IU/L)	1.2	<0.2-7.5	23	91
FSH (IU/L)	1.9	0.2-74	13	50
Cortisol (nmol/L)	524	441-966	10	50*
GH (mcg/L)	9.7	0.6-24	7	57*
IGF-1 (nmol/L)	14	<3.2-19	7	71
TSH (μIU/mL)	1.3	0.5-4.1	9	11
FT4 (pmol/L)	10.3	7.7-19.0	9	56
FT3 (pmol/L)	2.0	0.3-2.7	6	67

N refers to the number of men with results reported for the parameter.

% Outside reference range denotes below reference range except *above reference range.

BMI, Body mass index; T, testosterone; LH, luteinizing hormone; FSH, follicle-stimulating hormone; GH, growth hormone; IGF-1, insulin-like growth factor-1; TSH, thyroid stimulating hormone; FT4, free thyroxine; FT3, free triiodothyronine.