Bacheloroppgave

NTNU
Norges teknisk-naturvitenskapelige universitet
Fakultet for medisin og helsevitenskap
Institutt for nevromedisin og bevegelsesvitenskap

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Relative Energy in Sports: Impact on Reproductive Health in Female and Male Endurance Athletes

Bacheloroppgave i Human Movement Science
Veileder: Dionne A. Noordhof
Mars 2024

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Abstract

***Purpose*:** The study aims to investigate sex differences in Relative Energy Deficiency in Sport (REDs) and analyze its effect on reproductive ability among endurance athletes. The assessed parameters include resting metabolic rate (RMR) and levels of testosterone (TES), estrogen (E2), free triiodothyronine (T3), cortisol, luteinizing hormone (LH), and follicle-stimulating hormone (FSH) in venous blood samples. ***Method*:** The PubMed database was used to identify nine research articles, which were included based on predefined inclusion and exclusion criteria. ***Results*:** REDs can negatively impact sex hormones in endurance athletes. Determining appropriate energy availability levels depends on individual factors, making standardized thresholds for diagnosing REDs unrealistic. Future research should involve long-term studies with male and female athletes of different ages and performance levels.

***Keywords*:** Fertility, reproduction, low energy availability, sex hormones, sex differences, testosterone and estradiol.

Abstrakt

Formål: Studien tar sikte på å undersøke kjønnsforskjeller i relativ energitilgjengelighet i idrett (REDs) og analysere dets effekt på reproduktiv evne blant utholdenhetsutøvere. De vurderte parameterne inkluderer hvilemetabolsk rate (RMR) og nivåer av testosteron (TES), østrogen (E2), fri triiodotyronin, kortisol, luteiniserende hormon (LH) og follikkelstimulerende hormon (FSH) i venøse blodprøver. ***Metode**:* PubMed-databasen ble brukt til å identifisere ni forskningsartikler, som ble inkludert basert på forhåndsdefinerte inklusjons- og eksklusjonskriterier. ***Resultater:*** REDs kan påvirke kjønnshormonene negativt hos utholdenhetsutøvere. Å fastslå passende nivåer av energitilgjengelighet avhenger av individuelle faktorer, som gjør en universell grense for diagnostisering av REDs urealistisk. Fremtidig forskning bør involvere longitudinelle studier med mannlige og kvinnelige idrettsutøvere på ulik alder og prestasjonsnivå.

Nøkkelord: Fertilitet, reproduksjon, lav energitilgjengelighet, kjønnshormoner, kjønnsforskjeller, testosteron og østrogen.

Introduction

Optimum performance is crucial in sports. For endurance athletes, their physiological state plays a significant role in achieving success. There is a complex relationship between energy intake, training load, weight as well as psychological factors (Raastad et al., 2011). The intense focus on performance may lead to making choices that harm health, whether consciously or unconsciously. Relative Energy Deficiency in Sports (REDs) is a multifactorial syndrome where low energy availability (LEA) is a prominent factor (Mountjoy et al., 2023). LEA is a condition where athletes do not consume enough energy to support normal physiological functions. The body prioritizes available energy for daily activities such as training and competition, while it reduces the energy necessary to support basic biological processes like growth and reproduction (Sandbakk et al., 2023). An athlete may deliberately provoke LEA but can also occur unconsciously and is more prevalent in weight-sensitive sports (Raastad et al., 2011).

Originally stemming from the female athlete triad, REDs were initially believed to affect female athletes primarily. The International Olympic Committee (IOC) introduced REDs in 2014 based on research on LEA, acknowledging that male athletes are also vulnerable (Mountjoy et al., 2023). Research on men has identified similar negative metabolic and endocrine changes, including reductions in testosterone levels, reproductive dysfunction, decreased performance, injuries, and weakened bone health (Heikura et al., 2018; Nattiv et al., 2021).

The relationship between LEA, menstrual disturbances, and bone health in the female athlete triad has long been established. The HPA-axis, composed of the hypothalamus, pituitary gland, and adrenal glands, regulates the body's response to stress, including the stress coming of LEA. During stress, the hypothalamus releases corticotropin-releasing hormone (CRH), which stimulates the pituitary gland to secrete adrenocorticotropic hormone (ACTH) into the bloodstream. ACTH activates the adrenal glands to release cortisol, which in turn induces physiological changes to manage stress. Also, the HPA-axis is involved in the reproductive system through interaction with the HPG-axis (Hypothalamus-pituitary-gonadal axis), which regulates reproductive hormone production (Joseph and Whirledge, 2017).

REDs can cause a range of menstrual disturbances in female athletes, varying in severity from mild to complete absence of menstruation. The degree of reduction in estrogen and progesterone will affect their reproductive health (Sandbakk et al., 2023). Reduced testosterone levels may indicate underlying health issues, but this is not necessarily synonymous with poor health (Løvås and Husebye, 2017).

Hypogonadism refers to reduced hormone production in the gonads, which includes testes for males and ovaries for females. In females, this condition may cause oligomenorrhea or amenorrhea, while men may experience reduced libido and erectile dysfunction (Løvås and Husebye, 2017). Both males and females with hypogonadism are in increased risk of infertility. Secondary hypogonadism can be caused by diseases and medications, LEA, or overtraining (Stenqvist, 2021). The body regulates the production of sex hormones through the HPG-axis (see Figure 1). This system includes hormones such as luteinizing hormone (LH) and follicle-stimulating hormone (FSH), which are controlled by excretion from the hypothalamus in the brain. Both the hypothalamus and the pituitary gland are influenced by feedback from the sex hormones, contributing to maintaining a balanced hormone production in both males and females. Testosterone is the primary male hormone, while the main female hormones include gestagens (progesterone) and estrogens (Løvås and Husebye, 2017). Estradiol is the primary estrogen for reproductive function controlled by the HPG-axis (Hackney, 2023).

Among females, there is significant evidence that LEA promotes dysfunction in the hypothalamus-pituitary-gonadal axis (HPG-axis), while hormonal changes associated with exercise load are more difficult to interpret due to frequently overlooked menstrual variations (Hackney, 2023). Researchers have identified a condition which is associated with increased exercise loading over several years (Hackney and Hackney, 2005). It has been discovered that this can lead to a condition called "Exercise Hypogonadal Male Condition" (EHMC). This condition is prevalent among endurance athletes, observed by several researchers and characterized by low testosterone levels (Stenqvist, 2021). Changes in Triiodothyronine (T3) concentration may indicate metabolic dysfunction, making them a valuable marker for evaluating the effects of conditions like LEA and REDs.

The choice of research topic arises from a lack of knowledge about the consequences of REDs and LEA related to reproductive health in both female and male endurance athletes. In the present article, we will investigate how Relative Energy Deficiency in Sport affect reproductive health in female and male endurance athletes. Sex hormones ensure complex regulation of processes such as reproductive health, fertility and sex drive. This extends beyond reproductive capacity and impacts the physical aspects of sexual health and well-being throughout the lifespan, including the period after elite athletic careers.

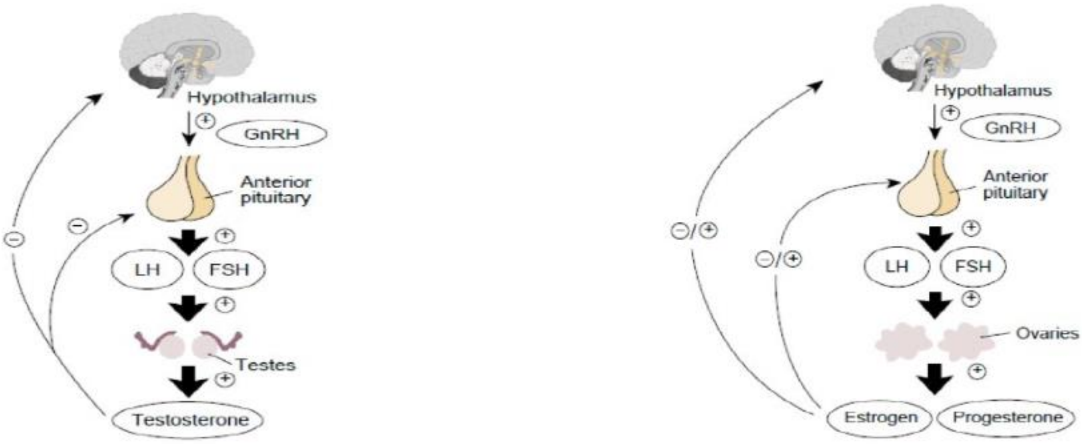

Figure 1. Illustration of males and females HPG-axis, (Logue et al., 2020)

Methods

Relevant literature was identified through searches in the PubMed database. The following search terms were employed:

- RED-S" AND "sex hormones" AND "athlete" NOT "review" gave 17 results.
- "LEA" AND "reproductive health" AND "athlete" NOT "review" gave 4 results.
- "LEA" AND "sex hormones" AND "athlete" NOT "review" gave 6 articles.
- "Exercise-hypogonadal male condition" AND "athlete" NOT "review" gave 5 results.
- "REDS" AND "reproductive health" AND "athlete" NOT "review" gave 7 results.

Some studies came as a result of more than one search combination. The selection of studies was guided by inclusion and exclusion criteria. Inclusion criteria were: 1) athletes active in endurance sports, 2) studies focusing on health aspects like fertility, menstrual function, or libido. Exclusion criteria were: 1) studies older than ten years, 2) studies that only included inactive subjects, and 3) studies not focusing on reproductive health and low energy availability, REDs, non-functional overreaching (NFOR), or overtraining syndrome. Additionally, a manual hand search was conducted in the reference lists of relevant studies to identify articles not captured during the initial search process. However, this did not result in the inclusion of additional studies. In total eight studies met our criteria; four studies included only male athletes; three studies included only female athletes; one study included both. There are limitations in the availability of high-quality studies that encompass both sexes.

Results

The present review includes eight main articles were all investigate hormone values in endurance athletes. Total number of participants was n=220, counting 116 females and 104 males. Excluded from the case study, the average number of included athletes was n=31.3. The total summation of reproductive dysfunctional athletes (low TES/MD) was n=77, excluded the experimental study of Jurov et al. (2022).

The effect of LEA on female reproductive function

When it comes to female reproductive health, LH and FSH are the first hormones released in the HPG-axis, leading to menstruation. Melin and colleagues (2015) was the only article that included LH values for females. Low and reduced EA (<45kcal/kg FFM/day) subjects were grouped (n=25) (see table 1). These subjects showed significantly lower LH than the optimal EA group ($p=0.009$). Even though there is a clear tendency for reduction in these hormones following reduced EA, all measurements were within reference ranges (Melin et al., 2015).

Heikura et al. (2018) showed severe differences in estradiol (E2) between reproductive functional (eumenorrheic) and unfunctional (amenorrhoeic) participants, while EA was not correspondingly different. Fahrenholtz et al. (2018) found E2 was significantly suppressed for all athletes. According to the authors, the correlations between E2 and energy deficit increased when energy deficit increased even more, see table 1. The study of Schaal et al. (2021) grouped subjects in well-adapted and non-functional overload based on participants performance outcome. Looking at estradiol, the values did not change significantly during the training overload in well-adapted athletes, while NFOR-athletes had significantly suppressed E2 throughout the whole menstrual cycle. Additionally, the luteal phase was shortened during training overload for this group($p<0.005$) (Schaal et al., 2021).

Schaal et al. (2021) found that ovarian function decreased even with short-term decreased EA, as shown in Table 1. Three articles present reduced T3 in MD groups compared with eumenorrheic athletes (Fahrenholtz et al., 2018; Heikura et al., 2018; Melin et al., 2015). The observational study by Heikura highlighted their amenorrhoeic female athletes had significantly lower levels of T3 and sex hormones compared to those with regular cycle, as per the results of the study ($p<0.05$). Melin shows somewhat significant result, despite only one athlete having considerably low T3-value, <1.2nmol/L. According to Fahrenholtz et al. (2018), athletes experiencing an energy deficit showed a slight tendency towards reduced T3 levels, despite having similar EA compared to other groups with energy deficit within a day. However, when dividing athletes into groups based on EA with 30kcal/kg FFM/day as the cut-off limit, none of the articles found any significant differences in T3 levels.

Table 1. Original studies that included female athletes.

Study	Participants	*n*	Study design	Interventions	Energy Availability (kcal/kg FFM/day)	Estradiol: pmol/L	Other hormones	Menstrual disturbances	EA where negative consequences start to appear
Melin *et al.* (2015)	National level endurance athletes. Age:26,2±5	40	Observational, longitudinal	Investigates association between EA and MD, with metabolism and REDs-associated conditions. 7 days recording. Low EA (n=8), reduced EA (n=17), optimal EA (n=15).	Optimal: 51.7 (48.1-55.3) Reduced: 38.5 (36.3-40.5). Low: 19.1 (11.6-26.6). 63% had reduced EA, <45kcal/kg FFM/day		T3 (nmol/L): Low EA:1.51±0.35. Reduced EA: 1.59±0.17. Optimal EA:1.64±0.29. (p<0.046). LH (IU/L): low+reduced EA:3.5±2.3. Optimal EA:6.6±3.6.	60% MD, EA:28.6±2.4. EMU EA:30.2 ± 1.8 kcal/kg FFM/day. (p <0.05)	RMR for MD+low EA:30.5±2.4 kcal/kg FFM/day. RMR for MD+optimal EA:27.6± 1.9 kcal/kg FFM/day (p=0.004),
Fahrenholtz *et al.* (2018)	Endurance athletes. Age:18-38.	25	Observational, longitudinal	7 days recording. Investigates time in energy deficit between MD (n=15) and eumenorrheic athletes (n=15). Relations to hormonal changes.	MD:35.6 ±11.6, EMU:41.3 ±12.7 kcal/kg FFM/day. (p=0.269)	WDEB<0kcal: r= -0.433 (p=0.034). WDEB <-300kcal: r=-0.516 (p=0.009).	T3: WDEB<0kcal: r=-0.360 (p=0.078) WDEB<-300kcal: r=-0.264 (p=0.203)	MD: n=15. Eumenorrheic: N=10.	
Schaal *et al.* (2021)	Runners: NFOR and well adapted. Age:21-33.	16	Experimental longitudinal	Compares EA in WA (n=9) and NFOR (n=7) athletes after a training overload. Investigates EA and changes in endocrine values between groups.	Baseline: WA:24.4±3.7. NFOR= 30.4±1.9. TO: WA:26.3±3.8 (p=0.170). NFOR:24.8±2.8 (p=0.041)	NFOR: luteal phase:4.7-28.5, mid-cycle:13.5-60.5, follicular phase:4.5-30.9 pmol/L. NFOR peak E2: Reduced (p<0.05)		Everyone eumenorrheic in baseline: d=24-35.	NFOR reduced E2: luteal (-47%) and follicular (-19%) phase to TO (p=0.047).
Heikura *et al.* (2018)	National or world-class endurance athletes. 35=females, 24=males.	59	Observational, longitudinal	7 days recording. Investigating EA and reproductive function. Investigate robustness criteria for REDs markers.	Low:24±6. Mod:38±8. MD:32±12, EMU:35±9.	Low EA:70±82, mod EA:85±73 MD:27±19, EMU:111±79. r=1.71	T3(pmol/L): MD:2.9±0.7. EMU:3.4±0.6. Low EA:3.1±0.6, mod EA:3.3±0.7.	MD: n=13. Eumenorrheic: n=22	

Presents values and details from articles including females. T3= triiodothyronine; LH=luteinizing hormone; WDEB= within day energy balance; EA= energy availability; MD= menstrual disturbances; EMU=eumenorrhea; NFOR=non-functionally overreach; TO=training overload; WA=well adapted

The effect of LEA on male reproductive function

Starting at the top of the HPG-axis also in males, two studies included LH and FSH in their analysis. Hooper and Zekarias' studies found trends of suppressed outcomes when EA was reduced. Hooper and colleagues found a marginal difference in LH and FSH values between EHMC endurance athletes and untrained control. However, this difference was not significant. However, this difference was not significant. The study reported two individuals with excessively suppressed LH levels below the reference range, these two also scored highest on the Aging Male symptoms (AMS) questionnaire. These individuals can be seen in conjunction with the case study, which found comparable results for their participants. The degree of LEA was unknown but based on the participants BMI (19 kg/m2) and testosterone levels, we can assume that the athlete underwent LEA. Additionally, the participant suffered from low libido. The authors specified LEA in endurance athletes may be an underlying factor for sexual health disorders (Zekarias and Shrestha, 2019).

Looking at low energy availability in male endurance athletes, there seems to be a significant association between LEA and reproductive function. Heikura et al. (2018) document a link among male long-distance runners compared to healthy, non-running controls, with a particularly large effect size (d=2.43). Stenqvist et al. (2021) strengthen the evidence, with the connection between LEA and reduced resting metabolic rate (RMR) among athletes at Olympic level. Hooper's study (2017) proves average testosterone concentrations were significantly lower in the EHMC group compared to the controls, with eight out of nine participants showing testosterone levels below the normal range, 12 nmol/L (Hooper et al., 2017).

Hooper's study observed that long-distance runners, averaging 81 ± 14 km per week, exhibited lower total testosterone levels (9.2 ± 2.3 nmol/L) compared to sedentary controls (16.2 ± 3.4 nmol/L), a statistically significant difference ($p < 0.001$). Additionally, the runners had lower energy availability (27.2 ± 12.7 kcal/kg FFM/day) compared to the control group ($p = 0.029$). Although serum testosterone concentrations were reduced in men regularly engaged in long-distance running compared to sedentary controls, Hooper suggests that some individuals may be more susceptible to low testosterone levels associated with high training due to genetic factors (Hooper et al., 2017).

The experimental study conducted by Jurov et al. (2022) experienced reduced T3 levels with the final reduction of energy availability (EA). Participants' hormonal status was monitored at each stage, with T3 levels decreasing after a 75% reduction. EA at this stage was as low as 8.82 ± 3.33 kcal/kg FFM/day, comparable to supressed testosterone levels. Both Stenqvist et al. (2021) and Heikura et al. (2018) identified the association between low testosterone levels and suppressed T3 levels in males. Stenqvist (2021) emphasized two individuals (5%) with subclinical low T3 (<4.3 pmol/L) who also exhibited several other clinical REDS markers.

Table 2. Original studies that included male athletes.

Study (author and year)	Participants	*n*	Study design	Interventions	Energy Availability measured, (kcal/kg FFM/day)	Testosterone (nmol/L)	Other hormones	EA where negative consequences start to appear
Zekarias and Shrestha (2019)	Competitive runner. Age:18.	1	Case study, observational longitudinal	One year follow up. Investigates EHMC-markers.		Total T: Baseline: 1.63nmol/L. 6 months: 16.3nmol/L. (Ref:10.4–41.6 nmol/L.)	LH:0.5 (ref:1.5-9.3) IU/L. FSH:1.8IU/L. (ref:1.5–9.3 IU/L)	12 later: BMI:19→26kg/m^2. Training volume decreased → EHMC symptoms disappeared.
Jurov *et al.* (2022)	Trained, well-trained, and elite endurance athletes.	18	Experimental, randomly controlled trial	Three steps energy of 14 days energy reduction: Stage 1: -25%. Stage 2: -50%. Stage 3: -75% EA.	Stage 1:22.4±6.1. Stage 2:17.3±5. Stage 3:8.82±3.33	Stage 2: 2.33±1.08 vs. 2.67±0.78. (P=0.026). r=-0.532. Stage 3: p=0.095.	T3: Stage 3: sign. reduced: 4.15±0.61 vs. 4.46±0.54 pmol/L. (p=0.072)	
Hooper *et al.* (2017)	Long-distance runners (n=9), non-active (n=8). Age:36±9.2.	17	Cross-sectional observational	Compares endocrine markers, body composition and EA between EHMC group and CONT.	EHMC: 27.2±12.7. CONT: 45.4±18.2. (p=0.029)	EHMC:9.2 nmol/L±2.3 CONT:16.2nmol/L±3.4. (p<0.001). Ref: 12nmol/L.	LH: EHMC= 3.76±2.1mU/mL. CONT:2.9 ± 0.6 mU/mL. (p=0.55). FSH: EHMC: 3.52±2.22IU/L. CONT:3.08±0.99IU/L	
Stenqvist *et al.* (2021)	Olympic-level athletes. Age: 24.7±3.8	44	Cross-sectional observational	Analyses endocrine markers and body composition. Giving score 1 or 0 if prevalence for REDs: low TES<14.8nmol/L, low T3<4.3pmol/L,	Low EA:23.6±1.8. Normal EA:30.4±3.3	Low: 16%, 12.9±5.3. Normal: 19.0±5.3nmol/L. Free testosterone: Low: 280±130pmol/L. Normal: 390±100pmol/L. p=0.061	T3: Low: 5.1±0.8. Normal: 5.7±0.7 pmol/L, p=0.127.	Low RMR: EA:23.6±1.8, TES:12.9±5.3nmol/L. 5/7 with low RMR → low TES.
Heikura *et al.* (2018)	National or world-class endurance athletes. 35=females, 24=males.	59	Observational, longitudinal	7 days recording. Investigating EA and reproductive function. Investigate robustness criteria for REDs markers.	Low: <30kcal/kg FFM/day. Mod: >30kcal/kg FFM/day. Low TES:31±12, normal TES:35±5 Low EA: 21±6, moderate EA: 37±4	Low TES: 40%, Low TES:15.1±3.0, normal TES:25.0±7.1. Low EA:14.8±3.6, moderate EA:22.9±8.0	T3pmol/L: Low TES:3.5±0.7, normal TES:4.0±0.6. Low EA:3.4±0.8, moderate EA:3.9±0.6	

Presents values and details from articles including males. T/TES=testosterone; LH=luteinizing hormone; FSH=follicle stimulating hormone; T3=triiodothyronine; EHMC=exercise- hypogonadal male condition;

Sex differences related to the effect of LEA on reproductive function.

Further, we will look at what the EA was for participants who showed low sex hormone concentrations. Melin found that 60% of their female athletes had MD, which correlates with 63% categorized with EA<45kcal/kg FFM/day. LH was significantly suppressed for the low EA group compared with the optimal group. Melin mentions MD participants with low EA had lower RMR than MD athletes with optimal EA. Fahrenholtz et al. (2018) showed no difference in EA between MD and EMU athletes. This study showed the highest EA for an MD group (35.6 ±11.6 kcal/kg FFM/day). Further, there was observed greater difference between EA in MD and EMU groups in Heikura's study (2018). The lowest female EA in this review was observed in the studies by Heikura (2018) and Schaal (2021). Participants were amenorrhoeic in Heikura (2018) and eumenorrheic in Schaal (2021). Interestingly, this also demonstrates the lowest EA leads to functional reproductive system in females. See Table 1 for details.

Heikura et al. (2018) showed participants with low TES, sub.14.8pmol/L, showing the lowest EA for male participants. See table 2. Eight out of nine EHMC participants in Hooper et al. (2017), showed testosterone under-reference. The EA for this group was somewhat higher than for the comparable group in Heikura et al. (2018). Looking at Stenqvist et al. (2021), 16% (n=7) had low testosterone, using the same cut-off as Heikura's study. Stenqvist (2021) used RMR to describe energy conservation that leads to suppressed reproductive function among others, because of too low EA for sufficient bodily processes. EA in low TES and suppressed RMR-group was among the same in the studies by Stenqvist et al. (2021) and Heikura et al. (2018). The experimental study by Jurov et al. (2022) showed a correlation between EA and suppressed testosterone when EA was 50% reduced. TES got even more suppressed when EA was additionally reduced. Thereby Jurov and colleagues (2022) demonstrated EA reduction gave individual responses on testosterone concentration. Zekarias and Shrestha's (2019) case study did not include energy availability, but their participant had clinically low testosterone levels at baseline, and increased sex hormones reasonable after six months of reduced training and increased food intake. We can assume his EA increased during this time.

Discussion

Based on the included articles, we aimed to get insight into how REDs influence the reproductive system and identify differences between genders in response to energy deficiency in endurance athletes. Our main findings support that suppressed energy availability will influence hormone status in both genders, but earlier in female than in male athletes. Additionally, the individual aspect seems to have greater impact than assumed. Consequences on the menstrual cycle in females seem to be very dependent on time in energy deficit. Further, males' ability to handle the training volume due to earlier training history seems to be important.

Sex hormones for females

The most interesting finding looking at the females' sex hormones is that the concentration of the hormones and menstrual status vary across a continuum of EA. Still, eumenorrheic athletes measured higher EA than eumenorrheic in all studies including both groups. Demonstrated by Heikura et al. (2018), hormone concentrations and menstrual status correlates clearer with other REDs-markers than looking at energy availability. This variation in estradiol concentration suggests certain athletes possess stronger genetic reproductive systems. Thus, some athletes can train more without impacting their reproductive health. The athletes in Schaal (2021) ran 52.2±4km/week, while Heikura's (2018) athletes ran 115±23km/week. This contradiction presents a point for discussion whether it highlights some athletes have more robust reproductive systems due to genetics, because of differences in training load or different interventions.

Further, sex hormone concentrations (E2, LH, and FSH) were suppressed for MD/non-functional groups in all studies(Fahrenholtz et al., 2018; Heikura et al., 2018; Melin et al., 2015; Schaal et al., 2021). According to Heikura et al. (2018), hormone concentration provided more precise estimates for reproductive function than dividing by energy availability based on cut-off value at 30kcal/kg FFM/day. Schaal et al. (2021) discovered 19% reduction in EA and changes in menstrual cycle after four weeks of training overload in eumenorrheic athletes. That seemed to cause 47% declined estradiol suggesting E2 is sensitive to energy deficits/stress in the HPG-axis since the group failed to sustain EA. E2 levels measured for the NFOR-group matched E2 values in MD-groups in the other studies. A possible case could be that intervention longer than four weeks would have discovered loss of menstruation in the NFOR-group. The study of Melin et al. (2015) suggests continuous glucose availability is important for regular LH pulsation and further menstruation. This is supported by Fahrenholtz's study (2018) who suggests pulsation from the HPG-axis to the pituitary gland for realising hormones occurs hourly. Both Fahrenholtz et al. (2018) and

Schaal et al. (2021) address major deficits in EA and EB lead the body to a state of energy conservation leading to rapid change in female endocrine values. Suppressed E2 or LH alone may not cause menstrual imbalance, but they are a part of the complex interaction for well-functioning reproductive system (Hackney, 2023). This supports the theory that the stress related to LEA is the primary underlying mechanism disrupting the HPG-axis (Logue et al., 2020).

Sex hormones for males

Our main finding demonstrates the correlation between high training loads and reduced testosterone levels (Heikura et al., 2018; Hooper et al., 2017)**.** High training loads can lower testosterone levels, but such decreases usually stay within the normal physiological range and may not cause typical symptoms of REDs. This perspective is backed by Jurov et al. (2022) which highlights the significance of considering individual and contextual factors while interpreting testosterone samples in endurance athletes. The study conducted by Hooper et al. in 2017 showed that extensive endurance training results in reduced testosterone levels in comparison to healthy but inactive individuals. The effect is statistically significant, with a large effect size (d=2.43). This decrease in testosterone may be caused by a condition known as exercise-hypogonadal male.

Heikura et al. (2018) showed 8 out of 9 with Hypogonadal male condition have testosterone concentrations below 12 nmol/L, which has previously been proposed as the lower limit of the normal range for circulating testosterone (Arver and Lehtihet, 2009). A possible explanation for the low testosterone concentrations is the high proportion of ultramarathon runners in the selection. Due to the high amount of exercise, ultramarathon athletes have an increased risk of not meeting their nutritional needs (Costa et al., 2019). The studies observed a decline in testosterone levels in a total of 11 athletes, one of whom reached a critically low level classified as hypogonadism (<8 nmol/L). Nattiv et al. (2021) suggest that testosterone values from 8-12 nmol/L may indicate the condition of hypogonadism. However, there is debate whether it is necessary to lower threshold values as criteria for REDs. Hackney and Lane (2018) found a reduction in plasma concentrations of sex hormones and impaired reproductive function. Healthy male runners with ≥5 years of endurance training experience were compared to runners with <5 years of endurance training experience. According to the authors, EHMC does not appear to be related to REDs or overtraining and is considered a different condition than secondary hypogonadism (Hackney, 2020).

In line with Hooper, Stenqvist investigates whether there is a causal relationship between athletes with REDs markers and energy status among Norwegian male endurance athletes at the Olympic level. 16% of the sample had low RMR, where a majority of the participants had one or more REDs markers. The findings strengthen evidence for the association between LEA and RMR. The need for further investigation of athletes without low RMR with REDs markers may lead to new, interesting findings. It is important to note that the incidence of REDs may be underestimated due to a lack of awareness and diagnostic tools.

Our studies focused on short-term observations on consequences of REDs, for 4-5 days. It is unclear if 4 days are sufficient to observe subclinical changes. Future study design can be used to explore a potential relationship between RMR and LEA. A study will aim to introduce a new approach to understand, prevent, and manage the condition among athletes of different age, performance levels, and sports. The study will investigate the correlation between LEA and reduced reproductive function.

Sex differences in LEA

By comparing males' and females' responses to LEA, individualities such as genetics, training background, and years in sports will affect how well endurance athletes tolerate levels of energy availability and deficits. It is accepted that females’ reproductive system demands larger amounts of energy. Anyhow, our article supports earlier findings that endurance athletes are at increased risk of hormonal changes due to difficulties in maintaining EA when exposed to high training volumes (Mountjoy et al., 2023; Nattiv et al., 2007; Tenforde et al., 2016). The idea of the LEA threshold arising from the IOC-REDs consensus statement, found negative health consequences appear at EA 30 kcal/kg FFM/day(Mountjoy et al., 2023). This was based on sophisticated but short-term laboratory studies on sedentary females examining gradual changes in energy availability, disruptions of sex hormones, and changes in markers of bone turnover. This seems to not reflect a true level of safeguarding for an athlete´s health. However, recent data from clinical real-life research and short-term studies, have found challenges related to assessing the fragility of a simple, universal threshold. Significant variations related to health and performance concerns have been identified among individuals and sexes. Despite calculations guiding research interventions or observations, there are risks associated with establishing a definitive clinical threshold for LEA due to many moderating factors.

While the current threshold is proposed too high and needs to be reassessed, some of the included articles use the IOC limit as grouping criteria, which makes it easier to compare and discuss. Hormonal changes related to a lower threshold of EA will adversely affect the athlete both from a health and performance perspective (Ackerman et al., 2020; Hackney et al., 2023).

Five articles included T3 in their analyses, where all discovered reduced levels in controls/non-LEA/EMU compared to LEA/MD/low TES athletes. Concentrations were somewhat lower for females than males, and some individuals identified with clinically low levels. This proves that LEA affects several hormonal parameters, and T3 is a marker supporting other signs that an athlete is suffering from energy deficits.

It is difficult to assess the long-term consequences of LEA on reproductive health in a controlled setting. The findings suggest that exposure time should be considered along with factors such as severity and sex to assess whether the condition of REDs poses a health risk. With that said, mild symptoms will occur after a short period, while severe symptoms will occur after a longer period of LEA (Heikura et al., 2018). Recent research has indicated that males have different energy needs and tolerance for energy deficiency compared to females, supported by our results showing males do not experience reduced hormone values until lower EA. Males semes to tolerate lower energy availability better than females, due to biological differences between the sexes, such as metabolism and fat distribution (Holtzman and Ackerman, 2021). Additionally, the consequences seem to be harder to discover in males. The absence of menstruation in females is a sign of irregularities in the reproductive system easy to discover. This could explain the time gap before the male's condition came into the researcher's spotlight.
Independent of sex, REDs as a syndrome may be difficult to diagnose because of the continuum of symptoms and variables. A combination of physiological tests, prolonged screening of EA, training habits, and different observations are relevant (Logue et al., 2020). Short-term consequences and reproductive status are moreover reversible. Therefore, it is important to address upcoming symptoms as early as possible to be aware of potential challenges.

The body prioritizes energy for processes essential for living and shuts down processes such as reproductive function. Athletes with REDs may maintain body weight compromised on reproductive health, bone building, growth, and metabolism (Mountjoy et al., 2023; Nattiv et al., 2007). This makes the diagnosis of REDs even harder to determined. Maintaining access to nutrition and avoiding energy deficits throughout the day seems to be important to ensure stable hormone concentrations, especially in the context of training when energy expenditure is high. Deficits in EA will lead the female body to a state of energy conservation faster in females than in males due to the continuous pulsation of hormones necessary for menstruation (Fahrenholtz et al., 2018; Hackney, 2023; Mountjoy et al., 2023). Sandbakk et al. (2023) describe the lack of knowledge in both athletes and coaches. This explains the importance of research and communication in the sports fields. Knowledge and resources in a training environment are necessary for preventive action to be taken.

Study design, strengths, and limitations

Throughout the included studies, the participant group is homogenous with mostly endurance athletes, non-injured and around the same age. This makes comparisons of the articles somewhat valid. However, while the articles of Heikura (2018), Melin (2015) and Stenqvist (2021) included Olympians and elite athletes, Schaal(2021), Zekarias and Shrestha (2019) and Hooper (2017) included runners on lower level. Jurov (2022) had participants on all performance levels. The difference in competitive standards makes it harder to conclude for a specific population. Hooper et al. (2017) stand out by including non-active controls compared with athletes. Thereby, the results will probably show greater differences.

In experimental studies, results may be stronger and more precise due to controlled variables. Anyhow, the method of Jurov et al. (2022) reduces subjects' EA to an extreme level, combined with maintained training volume. The design must be discussed as it may lead to critical consequences for participants. This increases the risk of injuries, sickness, over-training, or disordered eating. However, the design could be reused with modifications for example by removing participants when experiencing symptoms of LEA. To some degree, Schaal et al. (2021) have the same ethical challenge. However, following their protocol with a recovery phase seems more sustainable and with reduced risk for negative outcomes. Anyways, regardless of how interesting the results are, there are ethical guidelines to consider when conducting human research (CIOMS, 2016). Elite athletes may be difficult to include in experimental studies, because of their intention to prioritize training for optimizing performance outcome.

By contrast, in observational studies, participants are not controlled, and confounding variables may be left out. This study design is credible because participants stay in a familiar environment so the actions of participants will be reliable.
At last, the reliability of the two cross-sectional studies is lower since measurements are a "snapshot" of athletes' states, and we cannot explain causalities. Nevertheless, they have in advantage the possibility to include many participants and are still easy to conduct.
Further, the only case study, Zekarias and Shrestha (2019), found convincing results in their athlete suffering from EHMC. Anyhow, one case is not enough to generalize, nor possible to detect measurement errors and ensure validity (Pripp, 2018).

Five out of eight studies use a day recording period to estimate EA (Fahrenholtz et al., 2018; Heikura et al., 2018; Hooper et al., 2017; Melin et al., 2015; Schaal et al., 2021). Out of the three last studies, Stenqvist et al. (2021) and Zekarias and Shrestha (2019) would have been more comparable with similar procedures, while this was not relevant following the experimental protocol of Jurov (2022). Self-reporting of EA is shown to be a potential source of mismeasurements. For example, Stubbs et al. (2014) reports 5-21% underestimation, while Byrne et al. (2005) registered 20% overestimation. It is not objective and requires time and commitment from the athlete. It is known people with strained relationship to eating are sub-reporters. But self-reporting is low-cost, and no high-tech knowledge is required. By contrast, recording throughout a week is more reliable than the alternative of a one-day snapshot. Heikura et al. (2018) concludes physiological measurements of EA, as screening tools and blood measurements, increase the internal validity and gives a great understanding of an athlete's health.

There is a limitation in this review that some hormonal markers are included in just a few articles. With few variables, measurement errors are difficult to detect, and studies are less comparable. For instance, Schaal et al. (2021) would have been more relevant by including multiple hormones.

Conclusion

Without doubt, REDs negatively impact sex hormones in both males and females. Individual variables play a crucial role in determining the necessary level of Energy Availability (EA) for athletes' reproductive health to be functional. Therefore, it would be unrealistic to establish standardized thresholds for EA to diagnose athletes with Low Energy Availability (LEA) or REDs due to significant individual differences. For future research, there is a need for long-term interventions that include both female and male athletes in similar environments.

References

Ackerman, K.E., Stellingwerff, T., Elliott-Sale, K.J., Baltzell, A., Cain, M., Goucher, K., Fleshman, L., Mountjoy, M.L., 2020. #REDS (Relative Energy Deficiency in Sport): time for a revolution in sports culture and systems to improve athlete health and performance. Br J Sports Med 54, 369–370. https://doi.org/10.1136/bjsports-2019-101926

Arver, S., Lehtihet, M., 2009. Current guidelines for the diagnosis of testosterone deficiency. Front Horm Res 37, 5–20. https://doi.org/10.1159/000175839

Byrne, N.M., Hills, A.P., Hunter, G.R., Weinsier, R.L., Schutz, Y., 2005. Metabolic equivalent: one size does not fit all. J Appl Physiol (1985) 99, 1112–1119. https://doi.org/10.1152/japplphysiol.00023.2004

Costa, R.J.S., Knechtle, B., Tarnopolsky, M., Hoffman, M.D., 2019. Nutrition for Ultramarathon Running: Trail, Track, and Road. Int J Sport Nutr Exerc Metab 29, 130–140. https://doi.org/10.1123/ijsnem.2018-0255

Council for International Organizations of Medical Sciences (CIOMS), 2016. International Ethical Guidelines for Health-related Research involving Humans. Council for International Organizations of Medical Sciences (CIOMS). https://doi.org/10.56759/rgxl7405

Fahrenholtz, I.L., Sjödin, A., Benardot, D., Tornberg, Å.B., Skouby, S., Faber, J., Sundgot-Borgen, J.K., Melin, A.K., 2018. Within-day energy deficiency and reproductive function in female endurance athletes. Scand J Med Sci Sports 28, 1139–1146. https://doi.org/10.1111/sms.13030

Hackney, A., Melin, A.K., Ackerman, K.E., Torstveit, M.K., Burke, L.M., Mountjoy, M.L., 2023. REDs alert: male athletes be wary and scientists take action! Br J Sports Med 57, 1066–1067. https://doi.org/10.1136/bjsports-2023-106719

Hackney, A.C., 2023. Sex Hormones, Exercise and Women: Scientific and Clinical Aspects. Springer Nature.

Hackney, A.C., 2020. Hypogonadism in Exercising Males: Dysfunction or Adaptive-Regulatory Adjustment? Front Endocrinol (Lausanne) 11, 11. https://doi.org/10.3389/fendo.2020.00011

Hackney, A.C., Hackney, Z.C., 2005. The exercise-hypogonadal male condition and endurance exercise training. Curr Trends Endocinol 1, 101–106.

Hackney, A.C., Lane, A.R., 2018. Low testosterone in male endurance-trained distance runners: impact of years in training. Hormones (Athens) 17, 137–139. https://doi.org/10.1007/s42000-018-0010-z

Heikura, I.A., Uusitalo, A.L.T., Stellingwerff, T., Bergland, D., Mero, A.A., Burke, L.M., 2018. Low Energy Availability Is Difficult to Assess but Outcomes Have Large Impact on Bone Injury Rates in Elite Distance Athletes. Int J Sport Nutr Exerc Metab 28, 403–411. https://doi.org/10.1123/ijsnem.2017-0313

Holtzman, B., Ackerman, K.E., 2021. Recommendations and Nutritional Considerations for Female Athletes: Health and Performance. Sports Med 51, 43–57. https://doi.org/10.1007/s40279-021-01508-8

Hooper, D.R., Kraemer, W.J., Saenz, C., Schill, K.E., Focht, B.C., Volek, J.S., Maresh, C.M., 2017. The presence of symptoms of testosterone deficiency in the exercise-hypogonadal male condition and the role of nutrition. Eur J Appl Physiol 117, 1349–1357. https://doi.org/10.1007/s00421-017-3623-z

Joseph, D.N., Whirledge, S., 2017. Stress and the HPA Axis: Balancing Homeostasis and Fertility. International Journal of Molecular Sciences 18, 2224. https://doi.org/10.3390/ijms18102224

Jurov, I., Keay, N., Rauter, S., 2022. Reducing energy availability in male endurance athletes: a randomized trial with a three-step energy reduction. J Int Soc Sports Nutr 19, 179–195. https://doi.org/10.1080/15502783.2022.2065111

Logue, D.M., Madigan, S.M., Melin, A., Delahunt, E., Heinen, M., Donnell, S.-J.M., Corish, C.A., 2020. Low Energy Availability in Athletes 2020: An Updated Narrative Review of Prevalence, Risk, Within-Day Energy Balance, Knowledge, and Impact on Sports Performance. Nutrients 12, 835. https://doi.org/10.3390/nu12030835

Løvås, K., Husebye, E.S., 2017. Endokrinologi, 2. utg. ed. Gyldendal akademisk, Oslo.

Melin, A., Tornberg, Å.B., Skouby, S., Møller, S.S., Sundgot-Borgen, J., Faber, J., Sidelmann, J.J., Aziz, M., Sjödin, A., 2015. Energy availability and the female athlete triad in elite endurance athletes. Scand J Med Sci Sports 25, 610–622. https://doi.org/10.1111/sms.12261

Mountjoy, M., Ackerman, K.E., Bailey, D.M., Burke, L.M., Constantini, N., Hackney, A.C., Heikura, I.A., Melin, A., Pensgaard, A.M., Stellingwerff, T., Sundgot-Borgen, J.K., Torstveit, M.K., Jacobsen, A.U., Verhagen, E., Budgett, R., Engebretsen, L., Erdener, U., 2023. 2023 International Olympic Committee's (IOC) consensus statement on Relative Energy Deficiency in Sport (REDs). Br J Sports Med 57, 1073–1097. https://doi.org/10.1136/bjsports-2023-106994

Nattiv, A., De Souza, M.J., Koltun, K.J., Misra, M., Kussman, A., Williams, N.I., Barrack, M.T., Kraus, E., Joy, E., Fredericson, M., 2021. The Male Athlete Triad—A Consensus Statement From the Female and Male Athlete Triad Coalition Part 1: Definition and Scientific Basis. Clinical Journal of Sport Medicine 31, 335. https://doi.org/10.1097/JSM.0000000000000946

Nattiv, A., Loucks, A.B., Manore, M.M., Sanborn, C.F., Sundgot-Borgen, J., Warren, M.P., American College of Sports Medicine, 2007. American College of Sports Medicine position stand. The female athlete triad. Med Sci Sports Exerc 39, 1867–1882. https://doi.org/10.1249/mss.0b013e318149f111

Pripp, A.H., 2018. Validitet. Tidsskrift for Den norske legeforening. https://doi.org/10.4045/tidsskr.18.0398

Raastad, T., Helle, C., Garthe, I., 2011. Idrettsernæring. Gyldendal, Oslo.

Sandbakk, Øyvind, Staff, Hanne, Strøm-Sollli, Guro, 2023. Den kvinnelige idrettsutøveren (Trening, helse og prestasjon), 1st ed. Fagbokforlaget.

Schaal, K., VanLoan, M.D., Hausswirth, C., Casazza, G.A., 2021. Decreased energy availability during training overload is associated with non-functional overreaching and suppressed ovarian function in female runners. Appl Physiol Nutr Metab 46, 1179–1188. https://doi.org/10.1139/apnm-2020-0880

Stenqvist, 2021. Relative Energy Deficiency in Sport (RED-S) among Norwegian male athletes. University of Agder.

Stenqvist, T.B., Melin, A.K., Garthe, I., Slater, G., Paulsen, G., Iraki, J., Areta, J., Torstveit, M.K., 2021. Prevalence of Surrogate Markers of Relative Energy Deficiency in Male Norwegian Olympic-Level Athletes. Int J Sport Nutr Exerc Metab 31, 497–506. https://doi.org/10.1123/ijsnem.2020-0368

Stubbs, R.J., O'Reilly, L.M., Whybrow, S., Fuller, Z., Johnstone, A.M., Livingstone, M.B.E., Ritz, P., Horgan, G.W., 2014. Measuring the difference between actual and reported food intakes in the context of energy balance under laboratory conditions. Br J Nutr 111, 2032–2043. https://doi.org/10.1017/S0007114514000154

Tenforde, A.S., Barrack, M.T., Nattiv, A., Fredericson, M., 2016. Parallels with the Female Athlete Triad in Male Athletes. Sports Med 46, 171–182. https://doi.org/10.1007/s40279-015-0411-y

Zekarias, K., Shrestha, R.T., 2019. Role of Relative Malnutrition in Exercise Hypogonadal Male Condition. Med Sci Sports Exerc 51, 234–236. https://doi.org/10.1249/MSS.0000000000001783

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