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Effects of estrogen and testosterone on resting energy expenditure in older men

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Abstract

The mechanisms by which sex hormones cause changes in body composition are unclear. Sex steroid deficiency might directly reduce energy expenditure/fat oxidation and thereby predispose to increased body fat. Alternatively, sex steroid deficiency could result in lean tissue loss and thus reduced energy expenditure. Our objective was to examine the independent and combined effects of acute testosterone and estrogen withdrawal on respiratory exchange ratio (RER) and resting energy expenditure (REE) in men. The objective of the study was to examine the independent and combined effects of acute estrogen and testosterone withdrawal on respiratory exchange ratio (RER) and resting energy expenditure (REE) in men. Fifty-four men age 50–80 years, BMI range of 17–35 kg/m² underwent a 3 week eugonadal run-in hormone treatment period involving suppression of endogenous sex steroids using letrozole and leuprolide acetate (Lupron®) while sex steroid concentrations were maintained with transdermal testosterone (T) and estradiol (E). A second Lupron® injection was then given and participants were randomized to one of the following four three-week treatment groups: Group A (–T, –E), Group B (–T, +E), Group C (+T, –E), and Group D (+T, +E). REE and RER were measured via indirect calorimetry before and after the three-week treatment period. Three-week suppression and/or repletion of estrogen or testosterone did not produce changes in RER or REE within or between groups. We conclude that abrupt changes in sex steroids does not change resting substrate oxidation, indicating that changes that can be observed after more prolonged periods of deficiency are most likely due to direct effects of sex steroids on body composition.

Key terms

leuprolide acetate; indirect calorimetry; respiratory exchange ratio

Introduction

Decreases in sex steroid production that accompany aging may contribute to decreases in lean body mass and increases in fat mass (1–3). With aging, resting energy expenditure (REE), which makes up a significant amount of total daily energy expenditure, also decreases. Although changes in body composition contribute to changes in REE and substrate oxidation, changes in REE and substrate oxidation can occur prior to changes in body composition, such as seen in response to growth hormone replacement (4). If a similar process takes place with sex steroids, reductions in REE and/or changes in substrate oxidation would cause greater fat accumulation. To test this hypothesis it is necessary to measure these parameters prior to body composition changes, which is difficult in the setting

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of gradual declines in sex steroids that occur naturally. To overcome this problem we chose a model of acute sex steroid withdrawal and timed the indirect calorimetry measurement to occur before significant changes in body composition could take place. We elected to measure REE and the respiratory exchange ratio (RER – an index of substrate oxidation) after a 3 week period of sex hormone suppression/repletion. If no changes in RER or REE could be detected after 3 weeks of abrupt decreases in sex steroids this would strongly suggest that sex steroids affect body composition, which in turn affect REE rather than the other way around.

Materials and Methods

Protocol

Written informed consent was obtained from 60 individuals with 54 participants completing the study. All participants were healthy, 50–80 years of age, with a BMI of 17–35 kg/m².

On entry into the study, participants were given an intramuscular injection of 7.5 mg of the GnRH agonist leuprolide acetate (Lupron depot; Takeda Chemical Industries, Osaka, Japan). The participants simultaneously received 2.5 mg/d of letrozole (Femara; Novartis, East Hanover, New Jersey USA), 5 g/d of testosterone via gel (AndroGel; Unimed Pharmaceuticals, Buffalo Grove, IL), and 0.0375 mg/d of estrogen via patch (Vivelle; Novartis, East Hanover, New Jersey, USA), as previously described (5). After this three week run-in period, participants received a 2nd dose of leuprolide acetate and were randomized to four groups: Group A (–T, –E) discontinued the testosterone gel and estrogen patch, Group B (–T, +E) discontinued the testosterone gel only, Group C (+T, –E) discontinued the estrogen patch only, and Group D (+T, +E) continued on both the testosterone gel and estrogen patch. Estrogen and testosterone were measured using radioimmunoassay (RIA) (Diagnostic Products Corporation, Los Angeles, CA). Indirect calorimetry measurements were conducted after the run-in period (prior to randomization) and after three weeks of hormone repletion/suppression. Reliable determination of REE was conducted as previously described (6). Briefly, indirect calorimetry (DeltaTrac Metabolic Cart, Yorba Linda, CA) measurements were conducted over a 30 minute period after a 12 h fast and after a 30 minute period of bedrest (6).

Statistics

We based our power calculation from a study that employed Lupron® to suppress gonadal function for 10 weeks in men. They reported an average decrease in fat free mass of 2.1 kg and an increase in fat mass of 1.1 kg (7). The differences in energy expenditure that would cause this change in body composition were estimated as follows: An average gain of 1.1 kg of fat equals the retention of 8470 Kcal (1.1 kg × 7700 Kcal/kg fat) and the loss of 2.1 kg of lean tissue provides 2770 Kcal of energy (2.1 kg FFM × 1320 Kcal/kg lean tissue) for a net retention of 5700 Kcal over 70 days (~81 Kcal/day). The reproducibility of our indirect calorimetry has been reported (8) – at an average REE of 1719 Kcal/day the SD from 4 consecutive fasting measurements is 67 Kcal. Thus, if changes in REE (the major component of daily energy expenditure) were the source of the change in body composition equaling 81 Kcal/day, with an SD of 67 Kcal/day, our study with 12 men per group has at least 80% power to detect this effect size with an α of 0.05.

Comparisons of baseline characteristics were performed using a one-way analysis of variance (ANOVA) with post hoc Tukey test. Mixed model ANOVA was used to test whether between and within group differences exist in RER and REE. SPSS for Windows (version 12.0.0; SPSS Inc, Chicago, NC) and JMP (version 7.0.1; SAS Institute, Cary, NC)

were used for statistical analysis. Data are presented as mean $\pm$ SEM. Differences were defined as statistically significant at a p-value <0.05 .

Results

Participants who completed the study were well matched for age, weight and BMI (Table 1). As seen by the estradiol and testosterone concentrations, suppression or repletion of estrogen and/or testosterone to physiological levels was achieved (Table 1). Participants did not report any changes in activity or dietary patterns throughout the intervention. The 3 week suppression and/or repletion of estrogen or testosterone did not produce changes in RER or REE within or between groups (Table 1).

Discussion and Conclusion

Three weeks of individual or combined suppression of testosterone and/or estrogen in older men did not change REE and RER compared to maintenance of physiological concentration. These findings lead us to conclude that sex steroids are most likely to alter body composition directly rather than indirectly via changes in postabsorptive substrate oxidation. Others who have examined the effects of testosterone alone on energy and substrate metabolism over shorter periods of time also found no effect (9,10), whereas over longer periods of time increases in REE have been seen with testosterone replacement (11). We believe the present study is unique in that it examines the isolated and combined effects of physiological concentrations of testosterone and estrogen on REE and RER in a time frame short enough to avoid changes in body composition but long enough to be confident that detectable effects were not missed.

Body composition was not measured in this study because the three week period of sex hormone suppression is unlikely to produce detectable changes. Thus, while growth hormone replacement can increase REE before changes in body composition (4), it appears sex steroids have effects on REE primarily by changing body composition (7). The lack of effect of estrogen and testosterone on substrate oxidation indicate that changes in body composition that occur with falling sex steroid concentrations likely result from other sex hormone-associated perturbations in fat and muscle metabolism (12). Longer term supplementation studies have consistently shown the influence of estrogen and testosterone supplementation on body composition. Testosterone or estrogen therapy increases or maintains lean body mass and reduces the accumulation of subcutaneous and abdominal fat (2,3,13–15).

A limitation of this study is that we measured resting but not total daily energy expenditure. It is possible that sex steroids exert unique and specific metabolic effects on the other components of energy expenditure - thermic effect of food (TEF) or activity energy expenditure (AEE). However, we note that resting energy expenditure accounts for 60–70% of total daily energy expenditure in sedentary adults and we saw no hint of a trend for reductions in REE (in fact small, non-significant increases were seen in the sex steroid deficient groups). If acute sex steroid deficiency results in the estimated 80 Kcal/day energy imbalance (see power calculations) the lack of a decline in REE would mean that the TEF would have to fall by a remarkable ~50% to account for this change in energy balance or that AEE would need to decline. The latter could occur through changes in the efficiency of physical activity, which appears not to have been studied, or changes in the amount of physical activity. If reductions in physical activity occur they would more likely reflect effects of sex steroids on CNS regulation of this aspect of daily energy expenditure rather than a direct metabolic effect.

In summary, our findings indicate that estrogen, testosterone or estrogen plus testosterone do not independently change REE or overnight postabsorptive substrate oxidation. The effects of sex steroids on REE are most likely mediated by direct effects on body composition, either via direct effects on protein synthesis or via indirect effects on physical activity. Likewise, changes in metabolic rate with aging likely are not the direct result of changes in sex steroid concentration but rather due to body composition and perhaps other hormonal alterations. How the milieu of changing levels of sex steroids with aging perturbs fat or muscle metabolism, independent of energy metabolism, remains an important area of investigation.

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Table 1

Sex steroid concentrations, respiratory exchange ratio and resting energy expenditure before and after 3 weeks of hormone treatment.

	-T-E	-T+E	+T-E	+T+E
n	12	14	15	13
Age (y)	64.1±3.5	65.3±2.1	69.6±1.3	66.1±3.4
Weight (kg)	85.3±3.2	86.1±3.6	88.4±2.3	91.3±3.5
BMI (kg/m ²)	27.5±1.1	27.4±1.0	27.7±0.7	28.5±0.9
Estradiol (pg/mL)	0.1±0.0	38.9±6.4	0.1±0.0	22.2±2.8
Testosterone (ng/dL)	21.0±2.9	19.1±3.0	387.6±43.1	312.5±60.6
RQ _{t0}	0.84±0.01	0.83±0.02	0.84±0.01	0.84±0.02
RQ _{t3}	0.87±0.02	0.81±0.01	0.84±0.01	0.83±0.02
RQ _Δ	0.03±0.02	-0.02±0.02	0.01±0.01	-0.00±0.02
REE _{t0} (Kcal/d)	1648±69	1612±63	1655±65	1815±71
REE _{t3} (Kcal/d)	1674±61	1632±55	1683±52	1721±75
REE _Δ (Kcal/d)	27±62	20±52	29±45	-94±53

Values are shown as mean ± SEM. Subscripts t0 and t3 refer to time = 0 and 3 weeks of sex steroid deficiency and Δ refers to the change from week 0 to week 3. Estrogen and testosterone concentrations were not tested for statistical significance because they are not random variables.