Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Finkelstein JS, Lee H, Burnett-Bowie S-AM, et al. Gonadal steroids and body composition, strength, and sexual function in men. N Engl J Med 2013;369:1011-22. DOI: 10.1056/NEJMoa1206168

Table of Contents

Supplementary Appendix materials for Finkelstein JS et al., “Effects of gonadal steroids on body composition, strength, and sexual function in men”.

Inclusion criteria:

1. Age 20 to 50 years:

Exclusion criteria:

1. History of significant cardiac, renal, pulmonary, hepatic, benign prostatic hyperplasia, or malignant disease, current alcohol or illicit drug abuse, or major psychiatric disorders.
2. Current diagnoses of disorders known to affect bone metabolism including hyperthyroidism, hyperparathyroidism, osteomalacia, or Paget's disease.
3. Current use of medications known to affect bone metabolism including estrogens, androgens, anti-estrogens, bisphosphonates, denosumab, calcitonin, fluoride, oral or inhaled glucocorticoids, suppressive doses of thyroxine, lithium, pharmacological doses of vitamin D (greater than 2000 IU/day), or anti-convulsants.
4. Cognitive or intellectual impairment that precludes complete understanding of the study protocol.
5. History of deep vein thrombosis, pulmonary embolism, or clotting disorders.
6. Serum 25-OH vitamin D < 15 ng/mL
7. Serum PTH < 10 or > 65 pg/mL
8. Serum TSH < 0.5 or > 5.0 U/L
9. Serum calcium $\geq$ 10.6 mg/dL
10. Serum creatinine > 2 mg/dL
11. Serum AST or ALT > 2x the upper limit of normal
12. Serum bilirubin > 2 mg/dL
13. Serum alkaline phosphatase > 150 U/L
14. Plasma hemoglobin < 11 gm/dL.
15. Fracture within the last 6 months.
16. Serum testosterone level < 270 or > 1070 ng/dL
17. Serum PSA level > 4 ug/L.
18. History of violent behavior.

Physical Functioning, Vitality, and Overall Health.

Self-reported physical functioning, vitality, and overall health were assessed using a validated modification of the Short-Form General Health Survey.[1] All 3 measures declined significantly ($P<0.05$) (or exhibited a borderline ($P<0.1$) decline) compared with baseline values in men treated with placebo or 1.25 grams of testosterone daily in both cohorts, demonstrating an effect of testosterone on these measures (Table 2). The cohort-testosterone dose interaction terms for self-reported physical functioning ($P=0.258$), vitality ($P=0.370$), and overall health status ($P=0.075$) were not significantly different nor were the mean changes in these measures between groups receiving testosterone with or without aromatase blockade, suggesting that estradiol did not affect these measures.

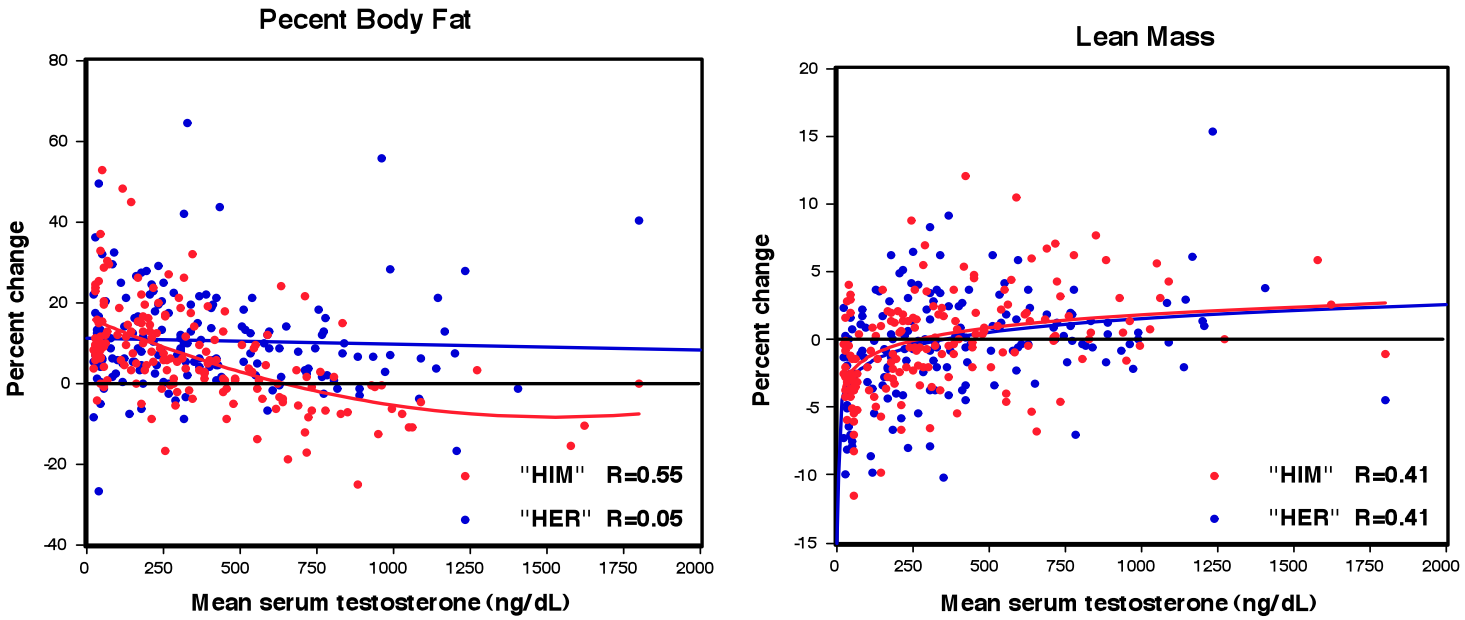

Figure S1. Serum Testosterone Levels versus Percent Change in Body Fat (upper panel) and Lean Mass (lower panel) Measured by DXA in Men Receiving Goserelin Acetate Plus 0 (placebo), 1.25, 2.5, 5, or 10 g of Testosterone Gel Daily Without Anastrozole ("COHORT 1" blue dots) or the Same Treatments Plus Anastrozole ("COHORT 2" red dots). For each subject the serum testosterone level represents the mean of values collected at weeks 4, 8, 12, and 16, unless the subject withdrew from the study before completion. The regression lines representing the best fit for "COHORT 1" and "COHORT 2" and the R values for each regression are shown.

There was a moderate to strong association between serum testosterone levels and the change in percent fat in "COHORT 1" (R=0.55) but virtually no significant relationship in "COHORT 2" (R=0.05). Because serum estradiol levels vary according to serum testosterone levels in "COHORT 1" but are very low in all subjects in "COHORT 2", these results provide strong evidence that fat accumulation in hypogonadal men is primarily, and possibly exclusively, due to estrogen deficiency.

In contrast, for lean mass there was a moderate association between serum testosterone levels and the change in percent fat in both "COHORT 1" (R=0.41) and in "COHORT 2" (R=0.41) and the regression curves were super-imposable. These results demonstrate that the relationship between the serum testosterone levels and the change in lean mass is not affected by the difference in estradiol levels in "COHORT 1" and "COHORT 2" and strongly support the conclusion that changes in lean mass in hypogonadal men are exclusively due to androgen deficiency.

Table S1: Number of subjects discontinuing study participation before completing the protocol and stated reasons for discontinuation in COHORT 1 and COHORT 2

Reason for dropping out	Number in "COHORT 1"	Number in "COHORT 2"
Symptoms of hypogonadism*	17	18
Changed mind	3	4
Too busy	1	4
Moved from area	3	1
Lost to follow-up	5	4
Mood swings	1	0
LFT's 2x normal (stopping rule)	3	3
Not specified	1	5
Other	2	5
Total	36	44

* Symptoms of hypogonadism included hot flashes, decreased libido, and/or fatigue.

Table S2. Initial and Final Scores (Mean ± SD) for Self-Reported Overall Health, Vitality, and Physical Functioning in Men in "Cohort 1" (top) and "Cohort 2" (bottom). For each scale, the maximum score is 100 points.

Testosterone Dose	Overall Health		Vitality		Physical Functioning	
	Initial	Final	Initial	Final	Initial	Final
0 grams/day						
COHORT 1 n=40	85.8 ± 10.1	77.0 ± 13.4*	73.7 ± 13.7	63.2 ± 20.6*	95.8 ± 9.4	86.3 ± 17.0†
COHORT 2 n=30	87.3 ± 10.1	76.2 ± 19.9*	75.8 ± 14.7	64.2 ± 25.1†	96.1 ± 6.5	84.4 ± 19.3*
1.25 grams/day						
COHORT 1 n=41	83.9 ± 14.1	70.7 ± 23.8*	73.7 ± 12.1	62.6 ± 25.0*	92.1 ± 15.4	86.2 ± 19.7
COHORT 2 n=32	88.3 ± 9.2	81.9 ± 9.7*	74.4 ± 13.3	67.5 ± 22.0∫	94.0 ± 9.8	88.8 ± 13.8†
2.5 grams/day						
COHORT 1 n=32	88.4 ± 11.7	82.7 ± 17.2	71.0 ± 15.4	70.0 ± 22.7	95.3 ± 9.0	92.5 ± 15.2
COHORT 2 n=38	84.1 ± 15.5	74.2 ± 19.3*	73.6 ± 14.7	66.7 ± 17.3±	94.7 ± 10.4	91.9 ± 10.6
5 grams/day						
COHORT 1 n=36	84.9 ± 15.6	84.1 ± 10.9	74.3 ± 13.6	68.4 ± 21.2	93.4 ± 15.9	90.1 ± 19.6
COHORT 2 n=40	88.2 ± 9.1	80.5 ± 15.4*	74.2 ± 13.8	70.2 ± 17.7	96.8 ± 6.2	91.2 ± 13.8†
10 grams/day						
COHORT 1 n=39	82.4 ± 18.8	81.8 ± 18.4	74.4 ± 16.9	75.2 ± 17.5	96.6 ± 9.5	94.2 ± 10.8
COHORT 2 n=35	87.6 ± 10.6	81.5 ± 14.2†	73.1 ± 13.9	69.5 ± 19.8	97.0 ± 6.5	90.4 ± 17.9∫

*=P<0.01 by paired t-test versus baseline value
†=P<.0.05 by paired t-test versus baseline value
∫=P<0.10 by paired t-test versus baseline value

REFERENCE

1. Cleary PD, Morrissey G, Oster G. Health-related quality of life in patients with advanced prostate cancer: a multinational perspective. Qual Life Res 1995;4:207-20.