Invecchiamento, fragilità e sistema endocrino

Intissar Sleiman
Some patients, despite advanced age and chronic comorbidities, may experience temporary disability related to illness or trauma, but rebound after recovery and return to their baseline.

Others may appear robust but tolerate medical stress poorly, and never regain full function following illness or hospitalization.

Still others are noted to have gradual but unrelenting functional decline in the absence of apparent stress factors.
Alas our frailty is the cause, not we for such as we are made of such we be.

William Shakespeare, Twelfth Night
Although cognitive decline may be found in frail persons, frailty resulting primarily from reduced cognition is considered a distinct clinical entity.
The frailty is more prevalent in women than in men.

Over the aging process, the trajectory of health and functional status is quite different in men and women.

Women tend to live longer than men but spend a larger portion of their life with disability and multiple chronic disease.
Cycle of frailty

Chronic Undernutrition
[Inadequate intake of protein and energy; micronutrient deficiencies]

- Neuroendocrine Dysregulation
- Anorexia of aging
- ↓ Total Energy Expenditure
- ↓ Activity
- ↓ Walking Speed
- Disability
- Dependency

- Resting Metabolic Rate
- ↓ Strength & Power
- ↓ VO₂max

Aging: Senescent musculoskeletal changes
- Negative Energy Balance
- Negative Nitrogen Balance
- Loss of muscle mass

Disease
- Weight Loss
- ↓ VO₂max

Source: J Gerontol Med Sci, 2001
We described old age as a chronic disease due to degeneration of the glands of internal secretions (hereinafter frequently referred to as the ductless glands), of the thyroid, the sexual glands, and the adrenals in particular.

Arnold Lorand
“Old Age deferred” 1910
Diabetes

- Normal Fasting Hepatic Glucose Output
- Decreased Insulin-Mediated Glucose Disposal
- Liver
- Brain
- Decreased Non Insulin Mediated Glucose Uptake
- Glucose Induced Insulin-Release
- Obese Diabetic
- Non Diabetic
- Thin Diabetic
- Visceral obesity
Hormones and frailty

T  testosterone
E  estrogen
GH  growth hormone
IGF-1  insulin growth factor 1
DHEA  dehydroepiandrosterone
Vit D  vitamin D.

OSTEOPOROSIS  SARCOPENIA
HIP FRACTURE

GH

↓ FUNCTION

FRAILTY

E

T

DHEA

ATHEROMA

HEART DISEASE

PERIPHERAL VASCULAR DISEASE
↓ MOBILITY
↓ ENDURANCE

T  E

T  E  Vit D

↓ COGNITIVE DECLINE

FUNCTION

T  E

Vit D
Endocrine changes with aging

• Pituitary- Gonadal function
  – Andropause
  – Menopause

• Hypothalamic-pituitary function
  – Somatopause (GH, IGF-I)
  – TSH
  – ACTH

• Adrenocortical function
  – Adrenopause (DHEA-DHEAS)
Andropause
Variation in serum total testosterone concentrations
Longitudinal effects of aging

![Graph showing longitudinal effects of aging on testosterone and free T index.](image)
The Androgen Deficiency in Aging Male Questionnaire

Yes  No  1. Do you have a decrease in libido (sex drive)?
Yes  No  2. Do you have a lack of energy?
Yes  No  3. Do you have a decrease in strength and/or endurance?
Yes  No  4. Have you lost height?
Yes  No  5. Have you noticed a decreased enjoyment of life?
Yes  No  6. Are you sad and/or grumpy?
Yes  No  7. Are your erections less strong?
Yes  No  8. Have you noticed a recent deterioration in your ability to play sports?
Yes  No  9. Are you falling asleep after dinner?
Yes  No  10. Has there been a recent deterioration in your work performance?

Note: A positive answer represents yes to 1 or 7 or any 3 other questions.
Clinical Consequences

- Sexual function
- Bone mineral density
- Muscle and fat mass
- Muscle strength
- Cognitive function
- Metabolic parameters
# Testosterone, Sex Hormone–Binding Globulin, and Frailty in Older Men

Beth A. Mohr, MS,* Shalender Bhasin, MD, † Varant Kupelian, PhD,* Andre B. Araujo, PhD,* Amy B. O’Donnell, MPH,* and John B. McKinlay, PhD*

<table>
<thead>
<tr>
<th>Table 4. Frailty at Wave 3 (T₃)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>T₃ Hormone</strong></td>
</tr>
<tr>
<td>Total T</td>
</tr>
<tr>
<td>Crude</td>
</tr>
<tr>
<td>Adjusted</td>
</tr>
<tr>
<td>Free T</td>
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<tr>
<td>Crude</td>
</tr>
<tr>
<td>Adjusted</td>
</tr>
<tr>
<td>SHBG</td>
</tr>
<tr>
<td>Crude</td>
</tr>
<tr>
<td>Adjusted</td>
</tr>
</tbody>
</table>

* Crude models contain a term for T₃ hormone and no other independent variables. Adjusted models are adjusted for age, diabetes mellitus, and depression; free testosterone (T) also adjusted for log caloric intake.

† Odds ratio (OR) for T₃ frailty expressed per 10 nM for total T, 0.1 nM for free T, and 10 nM for sex-hormone binding globulin (SHBG).

‡ P-value for test of null hypothesis that OR for hormone equals 1; Wald test.
Table 5. Differences In Total Testosterone (T), Free T, and Sex-Binding Hormone Globulin (SHBG) According to Frailty Component

<table>
<thead>
<tr>
<th>Frailty Component Hormone, nM</th>
<th>Frail According to Component</th>
<th>Unadjusted Mean</th>
<th>Age-Adjusted Mean</th>
<th>P-value*</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No</td>
<td>Yes</td>
<td>P-value*</td>
<td>No</td>
<td>Yes</td>
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<tr>
<td>Weight loss</td>
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<tr>
<td>Total T</td>
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<td>0.248</td>
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<tr>
<td>SHBG</td>
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<td>58.6</td>
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<td>Exhaustion</td>
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<tr>
<td>Total T</td>
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<td>.36</td>
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<td>47.8</td>
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<td>Physical activity</td>
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<tr>
<td>Total T</td>
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<td>.01</td>
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<tr>
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<td>0.239</td>
<td>.29</td>
<td>0.247</td>
<td>0.255</td>
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<td>49.4</td>
<td>61.7</td>
<td>&lt;.001</td>
<td>50.1</td>
<td>58.7</td>
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<td>Slow walking</td>
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<td>Total T</td>
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<td>.03</td>
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<td>Grip strength</td>
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<tr>
<td>Total T</td>
<td>14.9</td>
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<td>.008</td>
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<tr>
<td>Free T</td>
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<td>0.224</td>
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<tr>
<td>SHBG</td>
<td>51.1</td>
<td>52.7</td>
<td>.42</td>
<td>52.2</td>
<td>49.0</td>
</tr>
</tbody>
</table>

*Test of null hypothesis that mean hormone does not differ by frailty component.
Oral Testosterone Supplementation Increases Muscle and Decreases Fat Mass in Healthy Elderly Males With Low–Normal Gonadal Status

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2School of Physiotherapy, University of South Australia, Adelaide.
3Institute of Medical and Veterinary Science, Royal Adelaide Hospital, Australia.
4Division of Geriatric Medicine, Saint Louis University Medical School, and Geriatric Research, Education, and Clinical Center, Veterans Affairs Medical Center, St. Louis, Missouri.
Effects of Testosterone on Muscle Strength, Physical Function, Body Composition, and Quality of Life in Intermediate-Frail and Frail Elderly Men: A Randomized, Double-Blind, Placebo-Controlled Study


Context: Physical frailty is associated with reduced muscle strength, impaired physical function, and quality of life. Testosterone (T) increases muscle mass and strength in hypogonadal patients. It is unclear whether T has similar effects in intermediate-frail and frail elderly men with low to borderline-low T.

Objective: Our objective was to determine the effects of 6 months T treatment in intermediate-frail and frail elderly men, on muscle mass and strength, physical function, and quality of life.

Design and Setting: We conducted a randomized, double-blind, placebo-controlled, parallel-group, single-center study.

Participants: Participants were community-dwelling intermediate-frail and frail elderly men at least 65 yr of age with a total T at or below 12 nmol/liter or free T at or below 250 pmol/liter.

Methods: Two hundred seventy-four participants were randomized to transdermal T (50 mg/d) or placebo gel for 6 months. Outcome measures included muscle strength, lean and fat mass, physical function, and self-reported quality of life.

Results: Isometric knee extension peak torque improved in the T group (vs. placebo at 6 months), adjusted difference was 8.6 (95% confidence interval, 1.3–16.0; \( P = 0.02 \)) Newton-meters. Lean body mass increased and fat mass decreased significantly in the T group by 1.08 ± 1.8 and 0.9 ± 1.6 kg, respectively. Physical function improved among older and frailer men. Somatic and sexual symptom scores decreased with T treatment; adjusted difference was −1.2 (−2.4 to −0.04) and −1.3 (−2.5 to −0.2), respectively.

Conclusions: T treatment in intermediate-frail and frail elderly men with low to borderline-low T for 6 months may prevent age-associated loss of lower limb muscle strength and improve body composition, quality of life, and physical function. Further investigations are warranted to extend these results.

J Clin Endocrinol Metab, 2010
Potential harmful effects

- Prostate cancer
- Benign prostatic hyperplasia
- Sleep apnea
- Erythrocytosis
- Serum lipids
Recommendations

• In the absence of known pituitary or testicular disease, we suggest testosterone therapy only for men with unequivocally and reproducibly low serum testosterone concentrations (<200 ng/dL, 6.9 nmol/L) and clinically important symptoms of androgen deficiency. Physicians must discuss the uncertainty about the risks and benefits of testosterone therapy before recommending this approach.

• The target serum testosterone concentration in these men should be lower than that for younger men, for example, 300 to 400 ng/dL, rather than 500 to 600 ng/dL, to minimize the potential risk of testosterone-dependent diseases.

• If treatment is undertaken, the man should be screened before treatment and monitored during treatment for evidence of testosterone-dependent diseases.
Menopause
Declining follicle number with age

A comparison of the relationship between age and primordial follicle number in Block's study of 44 girls and women aged 7 to 44 years with that of Gougeon's study of women aged 45 to 55 years. Follicle depletion appears to accelerate in the decade preceding menopause.

Hormone levels

Mean daily levels of gonadotropins, sex steroids, and inhibins in older (ages 35-46 years; n=21), shown in red, and younger women (ages 20-34 years; n=23), shown in blue.
Clinical Consequences

- Bleeding patterns
- Hot flashes
- Sleep disturbance
- Sexual dysfunction
- Vaginal dryness
- Depression
- Breast pain
- Menstrual migraines
- Skin changes
- Joint pain
- Balance
- Bone loss
- Cardiovascular disease
- Dementia
Incidence of myocardial infarction by age and sex in a 26-year follow-up in the Framingham study. The incidence increases with age in both sexes, but occurs later (primarily after menopause) in women.
Six-year decrease in mean Mini-Mental State Examination (MMSE) score according to tertile of estradiol concentration in older women not taking hormone replacement therapy. Women with the highest levels of free estradiol and bioavailable estradiol (perhaps representing estradiol available to the brain) showed less cognitive decline over time.
In the Women's Health Initiative, combined estrogen-progestin therapy was associated with a significant increase in coronary events. CHD included nonfatal myocardial infarction and death due to CHD. The overall hazard ratio for CHD was 1.24 (nominal 95 percent confidence interval, 1.00 to 1.54).
Risk of dementia with combined estrogen-progestin therapy vs placebo

In the Women's Health Initiative Memory Study, after a mean follow-up of four years, HRT was associated with an increased risk of dementia (overall hazard ratio [HR] 2.05, 95 percent CI 1.21 to 3.48). Data shown only through five years of follow-up because numbers at risk are too small after this point for precise estimates.
In the Women's Health Initiative, combined estrogen-progestin therapy was associated with a significant increase in stroke when compared with placebo. The intention-to-treat hazard ratio was 1.31, 95 percent CI 1.02 to 1.68.
HRT increases pulmonary embolism

In the Women's Health Initiative, combined estrogen-progestin replacement therapy was associated with a significant increase in pulmonary embolism (8 more pulmonary emboli per 10,000 person years, HR 2.13, unadjusted 95 percent CI 1.39 to 3.25).
HRT increases invasive breast cancer

In the Women's Health Initiative, combined estrogen-progestin replacement therapy (red) was associated with a significant increase in invasive breast cancer (HR 1.24, unadjusted 95 percent CI 1.01 to 1.54) when compared with placebo (green).
Estrogen-progestin therapy reduces hip fracture

In the Women's Health Initiative, combined estrogen-progestin replacement therapy was associated with significant reduction in hip fracture (5 fewer hip fractures per 10,000 person-years, HR 0.7, unadjusted 95 percent CI 0.4 to 1.0).
Depression

BACKGROUND: Results of previous studies suggest that estrogen improves somatic and mild depressive symptoms experienced by perimenopausal women. This study investigated the efficacy of 17beta-estradiol for the treatment of clinically significant depressive disorders in endocrinologically confirmed perimenopausal women.

METHODS: Perimenopausal women (aged 40-55 years, with irregular menstrual periods and serum concentrations of follicle-stimulating hormone>25 IU/L), meeting criteria for major depressive disorder, dysthymic disorder, or minor depressive disorder, according to DSM-IV, were randomized to receive transdermal patches of 17beta-estradiol (100 microgram) or placebo in a 12-week, double-blind, placebo-controlled study. A 4-week washout period followed the 12-week treatment phase. Outcome measures were the Montgomery-Asberg Depression Rating Scale and Blatt-Kupperman Menopausal Index scores.

RESULTS: Fifty women were enrolled in the study; 26 met DSM-IV criteria for major depressive disorder, 11 for dysthymic disorder, and 13 for minor depressive disorder. Remission of depression was observed in 17 (68%) women treated with 17beta-estradiol compared with 5 (20%) in the placebo group (P = .001). Subjects responded similarly to estradiol treatment, regardless of DSM-IV diagnosis. Patients treated with estradiol sustained antidepressant benefit of treatment after the 4-week washout period, although somatic complaints increased in frequency and intensity. Treatment was well tolerated and adverse events were rare in both groups.

CONCLUSION: Transdermal estradiol replacement is an effective treatment of depression for perimenopausal women.
HRT reduces invasive colorectal cancer

In the Women's Health Initiative, combined estrogen-progestin replacement therapy was associated with a significant reduction in the cumulative hazard of invasive colorectal cancer (hazard ratio 0.56, unadjusted 95 percent CI 0.38 to 0.81).
Why ???

- The frailty is more prevalent in women than in men
- Over the aging process, the trajectory of health and functional status is quite different in men and women
- Women tend to live longer than men but spend a larger portion of their life with disability and multiple chronic disease
• We can hypothesized that frailty is more likely to develop in women because over the life span men reach a greater peak muscle and bone mass, hence resulting in a greater reserve.

• The rapid decline in estrogens in women at menopause may contribute to the rapid decline in bone mineral density, and the slight decline in androgens may lead to decreased lean body mass.

• The slower and less consistent decline in testosterone levels in men may contribute to delay the development of frailty

Med Clin North Am, 1999
Somatopause
Pattern of GH Secretion in younger and older women and men

J Clin Endocrinol Metab, 1987
Major components of the GH neuroregulatory system

Clin Interv in Ageing, 2008
Clinical features of the adult GHD syndrome

- ↑ Fat mass (especially abdominal fat)
- ↓ Lean body mass
- ↓ Muscle strength
- ↓ Cardiac capacity
- ↓ RBC volume
- ↓ Exercise performance
- ↓ Bone mineral density
- Atherogenic lipid profile
- Thin, dry skin; poor venous access
- Impaired sweating
- Psychosocial problems
  - Low self-esteem
  - Depression
  - Anxiety
  - Fatigue/listlessness
  - Sleep disturbances
  - Emotional lability and impaired self-control
  - Social isolation
  - Poor marital and socioeconomic performance
Effects of GH replacement in GHD adults

- ↓ Fat mass (especially abdominal fat)
- ↑ Lean body mass
- ↑ Total-body water and plasma volume
- ↑ Muscle mass strength
- ↑ Improved cardiac capacity
- ↑ Red blood cell volume
- ↑ Skin thickness
- ↑ Sweating
- ↑ Exercise capacity
- ↑ Resting energy expenditure
- ↑ Bone mineral density (after 1 yr of treatment)
- Altered lipid profile
  - Decreased total cholesterol
  - Decreased LDL-C
  - Decreased Apo B
  - Decreased triglycerides (if initially elevated)
  - Increased HDL-C (not seen in all studies)
  - Increased Lp(a)
- ↓↑ Insulin sensitivity (↓ acutely, ↑ after changes in body composition)
### Table 2. Effects of Treatments on Lean Body Mass and Fat Mass as Demonstrated by DXA

<table>
<thead>
<tr>
<th></th>
<th>Women</th>
<th></th>
<th></th>
<th></th>
<th>Men</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo (n = 14)</td>
<td>HRT (n = 14)</td>
<td>GH (n = 13)</td>
<td>GH + HRT (n = 16)</td>
<td>Placebo (n = 17)</td>
<td>Testosterone (n = 21)</td>
<td>GH (n = 17)</td>
<td>GH + Testosterone (n = 19)</td>
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<tr>
<td>Total lean body mass, kg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>35.7 (1.0)</td>
<td>36.7 (1.1)</td>
<td>36.8 (1.0)</td>
<td>35.8 (0.8)</td>
<td>57.0 (1.6)</td>
<td>51.5 (1.0)</td>
<td>54.4 (1.2)</td>
<td>52.7 (0.8)</td>
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<tr>
<td>26 Weeks</td>
<td>36.1 (1.1)</td>
<td>37.9 (1.0)</td>
<td>37.8 (0.9)</td>
<td>37.9 (0.8)</td>
<td>57.0 (1.4)</td>
<td>53.0 (1.1)</td>
<td>57.5 (1.3)</td>
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<tr>
<td>Change</td>
<td>0.4</td>
<td>1.2</td>
<td>1.0</td>
<td>2.1</td>
<td>0.1</td>
<td>1.4</td>
<td>3.1</td>
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<tr>
<td><em>P value for change vs placebo</em></td>
<td>.09</td>
<td>.001</td>
<td>&lt;.001</td>
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<td>.06</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
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<tr>
<td>Total body fat mass, kg</td>
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<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Baseline</td>
<td>28.4 (1.2)</td>
<td>25.7 (1.7)</td>
<td>27.8 (1.5)</td>
<td>22.6 (1.7)</td>
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<td>26 Weeks</td>
<td>28.1 (1.3)</td>
<td>25.1 (1.4)</td>
<td>25.3 (1.4)</td>
<td>20.8 (1.6)</td>
<td>25.0 (1.3)</td>
<td>22.2 (1.7)</td>
<td>21.1 (1.4)</td>
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<tr>
<td>Change</td>
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<td>-0.59</td>
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<td>-2.10</td>
<td>0.1</td>
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<td>.001</td>
<td>.006</td>
<td>.12</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
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*DXA indicates dual-energy absorptiometry; HRT, hormone replacement therapy; and GH, growth hormone. All mass values are reported as mean (SE). Baseline and week 26 data are crude values; change and *P* values are adjusted for age and initial value using the method of Dunnett.29

### Table 3. Effects of Hormone Administration on Total Body Strength

<table>
<thead>
<tr>
<th></th>
<th>Women</th>
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<th></th>
<th>Men</th>
<th></th>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Placebo (n = 13)</td>
<td>HRT (n = 13)</td>
<td>GH (n = 12)</td>
<td>GH + HRT (n = 13)</td>
<td>Placebo (n = 16)</td>
<td>Testosterone (n = 19)</td>
<td>GH (n = 15)</td>
<td>GH + Testosterone (n = 18)</td>
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<td>Baseline</td>
<td>108.0 (7.5)</td>
<td>111.8 (4.5)</td>
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<td>202.4 (9.9)</td>
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<tr>
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<td>104.9 (6.6)</td>
<td>115.9 (4.8)</td>
<td>109.2 (5.7)</td>
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<td>212.8 (7.0)</td>
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<tr>
<td>Change</td>
<td>-3.1</td>
<td>4.2</td>
<td>2.3</td>
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<td>6.2</td>
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<tr>
<td><em>P value vs placebo</em></td>
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<td>.29</td>
<td>.14</td>
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<td>.86</td>
<td>.28</td>
<td>.05</td>
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*Strength, reported as mean (SE), was measured in kilograms on 1-repetition maximum testing. HRT indicates hormone replacement therapy; GH, growth hormone. Baseline and week 26 data are crude values; change and *P* values are adjusted for age and initial value using the method of Dunnett.29

### Table 4. Effects of Hormone Treatments on Maximal Oxygen Capacity (VO2max) by Graded Treadmill Exercise Testing

<table>
<thead>
<tr>
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<th>Men</th>
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<tbody>
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<td></td>
<td>Placebo (n = 14)</td>
<td>HRT (n = 14)</td>
<td>GH (n = 12)</td>
<td>GH + HRT (n = 16)</td>
<td>Placebo (n = 17)</td>
<td>Testosterone (n = 21)</td>
<td>GH (n = 17)</td>
<td>GH + Testosterone (n = 18)</td>
</tr>
<tr>
<td>Baseline</td>
<td>21.4 (1.2)</td>
<td>22.9 (1.0)</td>
<td>23.1 (1.7)</td>
<td>21.7 (0.8)</td>
<td>28.1 (1.4)</td>
<td>26.5 (0.6)</td>
<td>28.2 (1.2)</td>
<td>26.9 (1.4)</td>
</tr>
<tr>
<td>26 Weeks</td>
<td>21.1 (0.9)</td>
<td>22.3 (0.9)</td>
<td>24.4 (1.6)</td>
<td>23.2 (0.7)</td>
<td>26.8 (1.4)</td>
<td>26.4 (0.9)</td>
<td>28.4 (1.4)</td>
<td>29.0 (1.4)</td>
</tr>
<tr>
<td>Change</td>
<td>-0.4</td>
<td>-0.4</td>
<td>1.4</td>
<td>1.3</td>
<td>-1.2</td>
<td>-0.4</td>
<td>0.3</td>
<td>2.3</td>
</tr>
<tr>
<td><em>P value vs placebo</em></td>
<td>&gt;.99</td>
<td>.07</td>
<td>.06</td>
<td></td>
<td>.49</td>
<td>.11</td>
<td>&lt;.001</td>
<td></td>
</tr>
</tbody>
</table>

*VO2max is reported as mean (SE) milliliters per minute per kilogram of body weight. HRT indicates hormone replacement therapy; GH, growth hormone. Baseline and week 26 data are crude values; change and *P* values are adjusted for age and initial value using the method of Dunnett.29
Common side effects

- Fluid retention; edema
- Arthralgias
- Carpal tunnel syndrome
- Decreased insulin sensitivity (acutely); hyperglycemia
Growth hormone (GH)—releasing hormone and GH secretagogues in normal aging: Fountain of Youth or Pool of Tantalus?

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Abstract: Although growth hormone (GH) is primarily associated with linear growth in childhood, it continues to have important metabolic functions in adult life. Adult GH deficiency (AGHD) is a distinct clinical entity, and GH replacement in AGHD can improve body composition, strength, aerobic capacity, and mood, and may reduce vascular disease risk. While there are some hormone-related side effects, the balance of benefits and risks is generally favorable, and several countries have approved GH for clinical use in AGHD. GH secretion declines progressively and markedly with aging, and many age-related changes resemble those of partial AGHD. This suggests that replacing GH, or stimulating GH with GH-releasing hormone or a GH secretagogue could confer benefits in normal aging similar to those observed in AGHD — in particular, could reduce the loss of muscle mass, strength, and exercise capacity leading to frailty, thereby prolonging the ability to live independently. However, while most GH studies have shown body composition effects similar to those in AGHD, functional changes have been much less inconsistent, and older adults are more sensitive to GH side effects. Preliminary reports of improved cognition are encouraging, but the overall balance of benefits and risks of GH supplementation in normal aging remains uncertain.

Keywords: growth hormone, growth hormone-releasing hormone, growth hormone secretagogues, aging, sarcopenia, frailty
Adrenopause
Changes in Levels of Serum Sulfated DHEA in Both Men and Women, According to Age.
DHEA and DHEA-S

- DHEA is converted to DHEA-S in the adrenal and liver, both of which contain a sulfotransferase.

- In the adrenal glands and peripheral tissues such as hair follicles, prostate, external genitalia, and adipose tissue, small amounts of DHEA and DHEA-S are converted to more active androgens such as androstenedione, androstenediol, testosterone, and 5-dihydrotestosterone, and estrogens such as estradiol and estrone. These hormones then exert their usual androgenic and estrogenic effects via the androgen and estrogen receptors, respectively.

- In women, adrenal production of DHEA and DHEA-S contributes substantially to overall androgen production and effects.

- In men the adrenal contribution is very small.
Although DHEA and sulfated DHEA are the most abundant steroids secreted from the adrenal cortex, when compared with their corticosteroid counterparts — cortisol and aldosterone — they remain something of an enigma.
It has been postulated that dehydroepiandrosterone (DHEA) and its sulfate ester, dehydroepiandrosterone sulfate (DHEAS), the major secretory products of the human adrenal gland, may be discriminators of life expectancy and aging. We examined the relation of base-line circulating DHEAS levels to subsequent 12-year mortality from any cause, from cardiovascular disease, and from ischemic heart disease in a population-based cohort of 242 men aged 50 to 79 years at the start of the study. Mean DHEAS levels decreased with age and were also significantly lower in men with a history of heart disease than in those without such a history. In men with no history of heart disease at base line, the age-adjusted relative risk associated with a DHEAS level below 140 micrograms per deciliter was 1.5 (P not significant) for death from any causes, 3.3 (P less than 0.05) for death from cardiovascular disease, and 3.2 (P less than 0.05) for death from ischemic heart disease. In multivariate analyses, an increase in DHEAS level of 100 micrograms per deciliter was associated with a 36 percent reduction in mortality from any causes (P less than 0.05) and a 48 percent reduction in mortality from cardiovascular disease (P less than 0.05), after adjustment for age, systolic blood pressure, serum cholesterol level, obesity, fasting plasma glucose level, cigarette smoking status, and personal history of heart disease. Our conclusions are limited by the single determination of DHEAS levels, but the data suggest that the DHEAS concentration is independently and inversely related to death from any cause and death from cardiovascular disease in men over age 50.
Longevity in healthy humans is associated with high levels of DHEA
The association between dehydroepiandrosterone and frailty in older men and women

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Key points

- The role of DHEA in frailty is uncertain, although low DHEA levels have been associated with increased rates of morbidity and mortality.
- In this cross-sectional analysis of a population of 898 older adult men and women, higher DHEAS levels were associated with fewer frailty characteristics.
- A body mass index > 30 kg/m² attenuated the association found between DHEAS levels and frailty.
- Further research will need to be done to ascertain whether the associations are due to similar conditions or whether lower DHEAS levels impact increasing frailty.
Effects of dehydroepiandrosterone (DHEA) on cardiovascular risk factors in older women with frailty characteristics

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Key points

- Older frail women were able to tolerate low-level exercise and DHEA supplementation (50 mg/day) for 6 months without significant adverse effects.
- DHEA supplementation (50 mg) increased hormone levels including DHEA-S, oestrone, oestradiol and testosterone levels in older frail women.
- Older frail women participating in a low-level exercise programme and receiving DHEA supplementation did not have significant changes in cardiovascular risk factors including lipid profiles, BP, body composition or fasting glucose.
Aging and Fountain-of-Youth Hormones

Paul M. Stewart, M.D.