Age-Related Endocrine Changes and the Role of Supplementation with GH, DHEA, and Melatonin

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Dietary Supplement Use in the Elderly, 1/14/2003
Dietary Supplements: DSHEA Definition

- Product intended to supplement the diet
- Contains one or more of the following:
  - A vitamin
  - A mineral
  - An herb or other botanical (not tobacco)
  - An amino acid
  - Any other dietary substance
- For oral intake as a concentrate, metabolite, extract, constituent, or combination
Rectangularization vs Extension of the Human Survival Curve

Maximum lifespan potential

Percent Survival

Age (Years)

Projected Future?
Present USA
1600's
50,000 BC?
To What Extent are the Observed Changes in Body Composition and Function with Aging Due to Decreases in GH and IGF-I?

Somatopause?

Courtesy of Michael Thorner, MD
24 Hour GH Secretory Profiles: Means (+ SD’s) at 20 min Intervals in 9 Young and 11 Healthy Old Men
Age-Related Blunting of Serum GH in Response to a Single Bout of Resistive Exercise in Healthy Men

(Marcell, et al., 1999)
Serum IGF-I Levels vs. Age in Healthy Women and Men in the BLSA

Women (n=131)

Men (n=258)

$r = 0.639 \ p < 0.001$

$r = 0.546 \ p < 0.0001$
Linear Segment Plots by Decade; Longitudinal Effects of Aging on Date-adjusted T and Free T Index.
Percentage of Group Hypogonadal by Decade Using Total vs Free T Index Criteria (n in group above bars)
### Similarities of Changes in Body Composition, Muscle Strength, Aerobic Capacity and Metabolic Variables with Aging and in Hormone Deficiency/Excess States

<table>
<thead>
<tr>
<th></th>
<th>Aging</th>
<th>Low GH</th>
<th>Low T or DHEA</th>
<th>High Cortisol</th>
<th>Low E2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lean Body Mass</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↑</td>
<td>—</td>
</tr>
<tr>
<td>Muscle Strength</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↑</td>
<td>—</td>
</tr>
<tr>
<td>Aerobic Capacity</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↑</td>
<td>—</td>
</tr>
<tr>
<td>Percent Body Fat</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Total and LDL</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Cholesterol</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin sensitivity</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↑</td>
<td>—</td>
</tr>
<tr>
<td>Glucose tolerance</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>
Effects of hGH Treatment on Body Composition, Skin Thickness and BMD in Men >60 Years of Age

Rudman, et al, 1990
The plural of anecdote is not evidence
**Study Design - Subjects and Interventions**

**Subjects:** Healthy women (n=53) and men (n=72), ages 65-88 y (mean, 72 y) with baseline age-related reductions in serum IGF-I (<230 ng/dl) and low to low normal gonadal steroid levels (women had had no exogenous estrogens for at least 3 months; men had total T levels < 470 ng/dl).

**Study Design:** Double-masked, placebo-controlled, randomized, non cross-over, 2x2 factorial

<table>
<thead>
<tr>
<th>Women</th>
<th>Men</th>
</tr>
</thead>
<tbody>
<tr>
<td>GH + HRT Placebo</td>
<td>GH + T Placebo</td>
</tr>
<tr>
<td>GH Placebo + HRT</td>
<td>GH Placebo + T</td>
</tr>
<tr>
<td>GH + HRT</td>
<td>GH + T</td>
</tr>
<tr>
<td>GH Placebo + HRT Placebo</td>
<td>GH Placebo + T Placebo</td>
</tr>
</tbody>
</table>

GH = rhGH 20 µg/kg s.c. 3x/wk in the p.m.
HRT = 100 µg/day E₂ patch + 2.5 mg/day MPA p.o.
T = 100 mg Testosterone enanthate i.m. every 2 wk
Hormone Levels in Men and Women Before and During Treatment

**Women**
- IGF-I (µg/L)
  - GH+HRT
  - GH
  - HRT
  - Placebo

**Men**
- Testosterone (nM/L)
- Estradiol (pM/L)

- GH+T
- GH
- T
- Placebo

Weeks
Effects of Hormone Administration on Lean Body Mass (DEXA) in Healthy Elderly Women and Men

![Graph showing percent change in lean body mass for women and men across different groups (Placebo, HRT, GH, GH+HRT for women; Placebo, T, GH, GH+T for men).](image-url)
Effects of Hormone Administration on Total Body Strength in Healthy Elderly Women and Men

Women

Men

GROUP

Percent Change

Placebo  HRT  GH  GH+HRT

Placebo  T  GH  GH+T

0.09  0.29  0.14

0.86  0.28  0.053
Effects of Hormones on Maximum Aerobic Capacity (ml O₂/min/kg BW) in Healthy Elderly Women and Men

**Women**

- Placebo: 1.000
- HRT: 0.073
- GH: 0.058

**Men**

- Placebo: 0.49
- T: 0.11
- GH: 0.0001

**GROUP**

Percent Change
Effects of Hormone Administration on Body Fat (DEXA) in Healthy Elderly Women and Men

**Women**
- Placebo
- HRT
- GH
- GH+HRT

**Men**
- Placebo
- T
- GH
- GH+T

Percent Change

- Placebo: 0.12, P < 0.0001
- HRT: 0.001
- GH: 0.006
- GH+HRT: 0.0001

- Placebo: 0.12, P < 0.0001
- T: 0.0001
- GH: 0.0001
- GH+T: 0.0001
Effects of Hormone Administration on Change in Subcutaneous and Visceral Abdominal Fat (MRI) in Healthy Elderly Women and Men

![Graphs showing changes in subcutaneous and visceral fat by group for women and men.](image)

**Women:**
- Placebo: 0.001
- GH: 0.008
- HRT: 0.046
- GH + HRT: 0.001

**Men:**
- Placebo
- GH
- T: 0.001
- GH + T

*Note: The graphs depict the percent change in fat content for each group, with error bars indicating variability. The p-values indicate statistical significance of the changes.*
Effects of Hormone Administration on Serum Levels of Total Cholesterol and Triglycerides in Healthy Elderly Women and Men

<table>
<thead>
<tr>
<th>Group</th>
<th>Percent Change Serum Cholesterol</th>
<th>Serum Triglycerides</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GH</td>
<td><img src="image" alt="Graph" /></td>
<td>.008</td>
</tr>
<tr>
<td>HRT</td>
<td><img src="image" alt="Graph" /></td>
<td>.042</td>
</tr>
<tr>
<td>GH + HRT</td>
<td><img src="image" alt="Graph" /></td>
<td>.046</td>
</tr>
<tr>
<td>Placebo</td>
<td></td>
<td>.006</td>
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<tr>
<td>GH</td>
<td><img src="image" alt="Graph" /></td>
<td>.046</td>
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<tr>
<td>T</td>
<td><img src="image" alt="Graph" /></td>
<td></td>
</tr>
<tr>
<td>GH + T</td>
<td><img src="image" alt="Graph" /></td>
<td></td>
</tr>
</tbody>
</table>
Effects of Hormone Administration on Serum Levels of LDL and HDL Cholesterol in Healthy Elderly Women and Men

**Women**
- Placebo: 0.001
- GH: 0.006
- HRT: 0.034

**Men**
- Placebo: 0.045
- GH: 0.038
- T: 0.008

**Percent Change**

**LDL Cholesterol**
- **Women**
  - Placebo
  - GH
  - HRT
  - GH + HRT
- **Men**
  - Placebo
  - GH
  - T
  - GH + T

**HDL Cholesterol**
- **Women**
  - Placebo
  - GH
  - HRT
  - GH + HRT
- **Men**
  - Placebo
  - GH
  - T
  - GH + T
Summary I

- GH (and testosterone) can:
  - Increase lean body mass
  - Increase muscle strength
  - Increase exercise capacity
  - Decrease body fat

- Combination of GH and sex steroids
  - Effects of GH and testosterone tend to be additive
  - Female hormones (HRT) and GH are not additive
Potential Risks of Hormone Treatments

- **Growth Hormone**
  - Arthritis
  - Carpal tunnel syndrome
  - Fluid retention
  - Hypertension
  - Diabetes
  - Cancers (?)
  - Accelerated Aging (?)

- **Female HRT**
  - Mastodynia
  - Vaginal Bleeding
  - Thrombosis
  - Cholelithiasis
  - Breast Cancer

- **Testosterone**
  - Prostate
    - Hyperplasia (BPH)
    - Cancer
  - Coronary Heart Disease
    - Decreased HDL
    - Increased LDL
  - Polycythemia
  - Minor
    - Acne
    - Sleep apnea
Frequency of Adverse Effects During Hormone Administration in Healthy Elderly Women

Fisher’s exact test vs placebo: * p < 0.05; † p < 0.01; ††† p < 0.0001
Frequency of Adverse Effects During Hormone Administration in Healthy Elderly Men

Fisher’s exact test vs placebo: * p < 0.05; † p < 0.01
Effects of Hormone Administration on Systolic and Diastolic BP Levels in Healthy Elderly Women and Men

Women

Men

GROUP

Percent Change

Systolic BP

Diastolic BP

Placebo  GH  HRT  GH + HRT  Placebo  GH  T  GH + T

†
Effects of Hormone Administration on Serum Glucose and Insulin Levels (GTT$_{120}$) in Healthy Elderly Women and Men

**Women**

- Placebo: Baseline glucose levels.
- GH: Increased glucose levels.
- HRT: Moderate glucose rise.
- GH + HRT: Significant rise in glucose levels.

**Men**

- Placebo: Baseline insulin levels.
- GH: Increased insulin levels.
- T: Minimal change.
- GH + T: Significant rise in insulin levels.

**Percent Change**

- Men: c, d
- Women: ‡‡‡‡, ‡, c, d

**Group**

- Placebo: Baseline measurements.
- GH: Glucose and insulin levels under GH.
- HRT: Glucose and insulin levels under HRT.
- GH + HRT: Glucose and insulin levels under GH + HRT.
- T: Glucose and insulin levels under T.
- GH + T: Glucose and insulin levels under GH + T.
Percent of Women and Men by Group with Fasting Glucose Values During Treatment Indicating Glucose Intolerance or Diabetes

Women

- Placebo
- GH
- HRT
- GH+HRT

Men

- Placebo
- GH
- TE
- GH+TE

Fasting Glucose Values (mg/dL):
- <110
- 110-126
- >126
What Are the Gaps in Clinical Knowledge?

- Are the declines in GH and DHEA with aging adaptive or maladaptive?
- Whom to study and treat?
  - Healthy elderly
  - Frail elderly
  - Disease Groups - CAD/CHF, Hip Fracture, hip/knee replacement, cancer cachexia, etc.
- Patterns of treatment
  - Prevention vs therapy
  - When to initiate, how long to continue?
  - Pattern - continuous vs discontinuous
  - Route - oral vs parenteral agents
  - Mode of Rx - GH, GHRH, GH secretagogues, DHEA(S)
Summary and Conclusions

- Treatment of older adults with GH has significant adverse effects which need to be balanced against potential benefits.
- GH may be a “pro-aging” hormone (mice):
  - Down-regulation of oxidative defense enzymes
  - Increase in oxidative tissue damage
- The true risk/benefit ratio and the treatment regimen to optimize this ratio are unknown.
Adrenal Steroidogenesis

Cholesterol

Pregnenolone

Progesterone

DHEA

Androstenedione

Testosterone

Estrone
Legal Definition of Androgenic Anabolic Steroids (1990)

- Chemical structure like testosterone
- Not an estrogen, progestin, or corticosteroid
- Pharmacological activity like testosterone
- Must promote muscle growth
**DHEA and Aging**

- Weak adrenal androgen
- DHEA most abundant steroid in humans
- Levels decrease 80% with aging; may contribute to many age-related declines
- In animal models, DHEA reverses features of aging
- Widely used as dietary supplement
- Safety and efficacy not established
Adverse Effects of Androgenic Anabolic Steroids

- Feedback inhibition of testosterone and sperm function
- Acne, male pattern hair distribution
- Prostate enlargement
- Increases in blood pressure, red blood cells, and clotting
- Decreased HDL/LDL, liver and cardiac dysfunction
- Virilization (women)
- Increased libido, aggressiveness, and appetite
DHEA: Background

- DHEA levels decrease after birth, and increase dramatically during puberty. DHEA is the most abundant steroid in adults. Non human primates have less DHEA than do humans and non primates have little or none.
- DHEA-S is conjugated by the liver.
  - DHEA t1/2 15-30 min, levels 2-4 ng/ml
  - DHEAS t1/2 7-10 hr, levels 2-6 µg/ml
- DHEA is converted from Δ-4 to Δ-3 androstenedione and then to active androgens and estrogens in liver, fat, muscle, prostate, bone, skin, and brain
- No definite DHEA receptor has been identified, BUT a compelling candidate has recently been reported (J Biol Chem 277: 21379, 2002)
DHEA: Background

- A weak adrenal androgen that exerts its effects after conversion to androgen and/or estrogen
- Most abundant steroid in humans; receptor not defined
- Levels decrease by 80% with aging, and may contribute to age-related declines in body composition, endocrine-metabolic, immune, neuropsychological, and cardiovascular functions
- Administration to old rats reverses or attenuates many features of aging
- Widely used as a dietary supplement for anti-aging and athletic enhancement purposes, efficacy and safety not established
Melatonin: Background

- Melatonin, N-acetyl-5-methoxytryptamine, is synthesized from serotonin in many tissues, primarily the pineal gland
- Circulating melatonin is inactivated in the liver, and its conjugates are excreted by the kidney
- The pineal gland is regulated by a circadian rhythm-generating system located in the hypothalamic SCN
- Measurement of melatonin in plasma and saliva is a measure of the biological clock
- Capillary GC-MS is gold standard assay
Melatonin: Background

- Numerous prior reports suggest that melatonin is produced during the dark phase of the day-night cycle and that there is an age-related diminution in nocturnal melatonin secretion.
- The bioavailability of melatonin in humans has not been well characterized.
- Use of an improved GC-MS assay, and PK studies, suggest that melatonin secretion occurs at a constant rate rather than in peaks, with onset in the evening until pineal synthesis ends in the early AM, does not correlate with the duration of the dark phase, and does not differ by gender or with advanced age.

(Fourtillan et al, Am J Physiol 280:E11, 2001)
Biological Research - It’s All “Natural”…!

“People can be induced to swallow anything, provided it is sufficiently seasoned with praise.”

Jean Moliere
Skepticism is the chastity of the intellect, and it is shameful to surrender it too soon or to the first comers.

G. Santayana (1923)