Longevity Medicine & the Endocrine System

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OBJECTIVES

- List 3 contributors to the aging process
- Briefly describe the changes in these systems with age: adrenal, pituitary, thyroid, reproductive
- Interpret the hormones frequently measured in the assessment of the aging endocrine systems
Is there a "fountain of youth"?

- Ponce de Leon searched for the "fountain of youth" in 1513
- Found Florida instead
Persons aged > 65 years constitute the fastest-growing segment of the U.S. population.

By 2030, 20% (or 70 million people) will be 65 or older.

There has been a greater than 30-year increase in life expectancy since 1900:
  - In 1900, median life expectancy was 47, in 2001 it was 77 years.

Most American women will spend the last 1/3 of their lives post-menopause.

More than one million of the Baby Boomers will live to be 100 years old.
What is aging?

- Physical decline
  - Abilities
  - Appearance
  - Impaired repair mechanisms
- Cognitive/emotional decline

“Quality of life issues”
The Causes of Aging*

- Wear and tear
- Silent inflammation
- Decline in hormone levels

*According to American Academy for Anti-aging Medicine (A4M)
Human Endocrine System

- **Endocrine Glands**
  - Glands that secrete hormones to regulate various functions of the body.

- **Hormones**
  - Chemical messengers
  - Receptors on target organs
  - Hormone/receptor elicit a physiological response
  - Regulated through “feedback loops”
**Endocrine Systems Involved in Aging**

- Thyroid
- Adrenals
  - Adrenopause
- Pituitary
  - Somatopause
- Reproductive:
  - Andropause
  - Menopause

In addition to each hormone’s primary function, most also contribute to promoting and supporting other endocrine systems, augmenting tissue repair and combating inflammation!
## The “Pauses” of Life

<table>
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<th>PAUSE</th>
<th>DECLINE IN</th>
<th>TYPICAL ONSET AGE</th>
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The Thyroid Gland

And aging…
Thyroid hormones regulate biochemical processes essential to growth and development including:
- Energy production from carbohydrates
- Cardiovascular function
- Nervous system reactivity
- Digestion

Decline begins at age 50
Thyroid hormone synthesis is controlled by the hypothalamus through a hormone called TRH (thyroid releasing hormone)
The measurement of various hormones that aid in the diagnosis of thyroid diseases and the assessment of function are:

- **TSH** - the pituitary hormone that stimulates the thyroid gland to produce T3 and T4
- **Free T3 and free T4**
  - Only free hormone is active
  - Total T4 - 99.97% bound and 0.03% Free T4
  - Total T3 - 99.7% bound and 0.3% Free T3
- **Anti-TPO** – autoantibody (thyroid peroxidase)
  - Positive TPO Ab’s may indicate an increased risk of future hypothyroidism*

**Hypothyroidism**

- **Distribution**
  - 98% of thyroid disease
  - Very common after age 50
- **Serious complications**
  - Heart failure
  - Coronary artery atherosclerosis
  - Anemia
  - Infertility
  - Increased susceptibility to infection
  - Psychiatric disorders
Thyroid Replacement Therapy

- Levothyroxine (T4) e.g. Synthroid
- T3
- Combination of both, e.g. Armour thyroid

TSH is the most accurate indicator for determination of the adequacy of hormone replacement therapy*

Support for the aging thyroid

Optimal function of the thyroid gland is essential to health
- Many issues attributed to menopause or aging are related to hypo-functioning thyroid

Supplements
- Iodine
- Vitamin Supplements
  - Vitamin A
  - Vitamin B complex (thiamine (B1), riboflavin (B2), niacin (B3), pantothenic acid (B5), pyridoxine (B6), biotin (B7), folic acid or folate (B9), cobalamin (B12))
  - Vitamin C
  - Vitamin D
  - Vitamin E
- Minerals
  - Selenium
  - Zinc
TSH Reference Intervals

- Previous guidelines suggest treating for hypothyroidism if TSH is > 6 µIU/mL
- Current reference range lists 3 µIU/mL as upper limit of normal (American Association of Clinical Endocrinologists) *
  - Many endocrinologists will treat if TSH >2.5 µIU/mL

The Pituitary Gland

And aging…
**Somatotropic Axis**

- **Neuroendocrine control**
  - GHRF stimulates
  - SRIF (somatostatin) inhibits - responsible for the pulsatile character

- **Other stimulating factors**
  - Neurotransmitters and neuropeptides
  - Hypoglycemia
  - Stress, intense physical exercise, sleep, fasting
  - Thyroid hormones
  - Sex steroid hormones

- **Negative feedback**
  - Direct: GH
  - Indirect: IGF-1 stimulates SRIF synthesis and inhibits GHRF
Biological Effects on Target Organs

- On the epiphyseal plate
  - stimulates the growth of long bones by its action on the epiphyseal cartilage
  - Activation by thyroid hormones
  - Sex hormones enhance the effect
  - Inhibition by glucocorticoids (e.g. Cortisol)

- Hypertrophy of muscle

- Anabolic hormone effect: enhances protein synthesis

- Anti-insulin effect: lipolysis, increases glycemia

- Phosphate and sodium retention

- Increases intestinal calcium absorption
Growth Hormone Decline
Laboratory Assessment of Pituitary Function

- Growth hormone
  - Direct measurement by immunoassay
  - Insulin stimulation test for diagnosis of GH deficiency
    - Insulin is administered IV
    - GH measured in timed blood samples

- Insulin-like growth factor 1 (IGF-1)
  - Less variability during the day
  - Available on microplate format
Growth Hormone as an “Anti-aging” Supplement

- Available at clinics and through prescription for adult GH deficiency.
  - Humatrope® (Somatropin, rDNA Origin, for Injection)
  - Protropin® (somatrem for injection),
- Many side effects
  - bloating, carpal tunnel syndrome, gynecomastia, insulin resistance, increase in blood pressure, and decrease in thyroid hormone production.
- Human GH injection treatments are very expensive
- Many different preparations, not always measured by GH immunoassays

Remember: Many hormones support GH release (thyroid, reproductive)
Adjusting other hormone levels could produce a similar effect!
The Adrenal Gland...
Adrenal Gland

- Located in retroperitoneal region, on superior surface of each kidney
- Each adrenal gland is separated into two distinct structures, the adrenal cortex and medulla
  - The cortex produces cortisol, aldosterone, and androgens
  - Medulla produces epinephrine and norepinephrine
- The combined weight of the adrenal glands in an adult human ranges from 7 to 10 grams
Adrenal Cortex

Medulla (epinephrine)

Zona reticularis (DHEA, DHEA-S)

Zona fasciculata (Glucocorticoids, e.g. Cortisol)

Zona glomerulosa (mineralocorticoids, e.g. Aldosterone)

Synthesis of Mineralcorticoids and Glucocorticoids

Cholesterol → Pregnenolone → Progesterone → Mineralcorticoids

17OHPreg → 17OHProg → Glucocorticoids

DHEA → Androstenedione → Androgens

(cortisol)

(Aldosterone)
DHEA

- Most abundant hormone in body
- Precursor of estrogen, progesterone, and testosterone
  - Produced predominately by the adrenals
  - Small amounts produced in primary sex organs, skin, and brain
- Production declines with age, peaks in the late 20’s
- By age 70, the body may make ¼ of the amount produced in the 20’s
- Anti-aging functions may include
  - Supports immune system
  - Maintenance/repair of tissues
  - Increase bone growth
  - Decrease cholesterol
  - Increase sense of well-being
- Supplements are sold OTC
Cortisol

- A life sustaining hormone essential to the maintenance of homeostasis
- Called the “stress hormone”
- Influences, regulates or modulates many of the changes that occur in the body in response to stress
- The only hormone in the body that increases with age!
Functions of Cortisol

- Blood sugar (glucose) levels
- Fat, protein and carbohydrate metabolism to maintain blood glucose (gluconeogenesis)
- Immune responses
- Anti-inflammatory actions
- Blood pressure
- Heart and blood vessel tone and contraction
- Central nervous system activation
Effects of Cortisol Overproduction due to Stress

- Receptors for many hormones have decreased sensitivity
  - Thyroid
  - Sex hormones
  - Insulin
  - Growth hormone

- Effects on bone: inhibits bone resorption
Chronic stress leads to higher and more prolonged levels of circulating cortisol.

This leads to:
- Impaired cognitive performance
- Dampened thyroid function
- Blood sugar imbalances, such as hyperglycemia
- Decreased bone density
- Sleep disruption
- Decreased muscle mass
- Elevated blood pressure
- Lowered immune function
- Slow wound healing
- Increased abdominal fat
Effects of Stress

Not only affects the adrenals but
The reproductive system also!
Adrenal Fatigue

- Ultimate result of stress leads to hypofunction
- Chronically low levels of circulating cortisol
- Results in/Causes
  - Brain fog, cloudy-headedness and mild depression
  - Low thyroid function
  - Blood sugar imbalances, such as hypoglycemia
  - Fatigue – especially morning and mid-afternoon fatigue
  - Sleep disruption
  - Low blood pressure
  - Lowered immune function
  - Inflammation
Laboratory Assessment of the Adrenals

- Cortisol levels
  - Am
  - Pm
- DHEA-S
- Measurement is primarily by immunoassay
Management of Adrenal Stress

- Reduce sources of stress
  - Lifestyle changes
    - Sleep
    - Exercise
    - Diet
- Supplementation
  - DHEA
  - Vitamins,
    - especially C, E, and B complex
  - Minerals
    - Ca, Mg, serine
The Endocrinology of Aging: Can We Turn Back the Clock?

Health Issues in the Aging Female
HORMONAL REGULATION: Female

Hypothalamic - pituitary - gonadal axis

Hypothalamus

GnRH

Pituitary

LH, FSH

Target organs (ovaries)

Steroids, Inhibin

Feedback

Steroids

(Estrogens, Progesterone)

Stimulation
**ESTRADIOL**

- Steroid hormone
  - Synthesized from cholesterol in the ovaries, placenta and adrenals
- Predominately bound to SHBG
- Function in females
  - Stimulates secondary sex characteristics
  - Causes proliferation of endometrium
  - Increases thickness of vaginal epithelium, vascularity of cervix, cervical mucous elasticity and dilates the cervix
  - The “nice” hormone, affects mood
- Decline causes many of the symptoms of menopause
PROGESTERONE

- Steroid hormone
  - Synthesized from cholesterol in the ovaries, placenta and adrenals

- Function
  - Preparation for pregnancy by thickening and vascularizing the endometrium
  - Induction of differentiation of the breast and support of lactation
  - Increase of basal body temperature

- One of the first hormones to decline in perimenopause
  - E2 and progesterone become unbalanced

- A mood calming hormone, assists in sleep
Perimenopausal transition
- Menstrual cycles
  - Irregular and may be anovulatory
- Hormone levels
  - FSH is increased
  - LH is normal
  - Estradiol and progesterone are decreased
  - AMH is decreased

Cessation of cyclic ovarian function that usually occurs in the fifth decade
- Symptoms caused by declining estradiol
- FSH and LH are greatly increased
  - FSH:LH ratio >1
Laboratory Assays Commonly Requested by Physicians for the Assessment of Women Nearing Menopause

- **Primary Assays**
  - Estradiol
  - Progesterone
  - LH, FSH
  - Prolactin
  - DHEA-S
  - Total testosterone
  - TSH
  - AMH

- **Helpful Assays**
  - SHBG
  - Measurement or calculation of free or bioavailable testosterone
POST MENOPAUSAL STATE

- Hormone levels
  - FSH and LH are greatly increased
    - FSH:LH ratio >1
  - Steroid hormone levels
    - Estrogens are markedly decreased
    - Androgens are slightly decreased
  - Anti-Mullerian Hormone (AMH) levels are negligible
    - Can AMH levels predict age at menopause?
AMH levels and # of follicles

Follicle Number and Female Age

- Birth
- Optimal Fertility
- Decrease Fertility
- End of Fertility
- Irregular Cycles
- Menopause

Te Velde et al. Mol Cell Endo 1998;145:67-73
Do we need to be able to predict menopause?
Menopausal symptoms are usually divided into three categories:

- Vasomotor symptoms: hot flashes, night sweats
- Somatic symptoms: headaches, joint pain
- Psychological symptoms: depression, irritability

Most symptoms result from:

- Declining hormones (estradiol, progesterone, testosterone)
- Imbalance of hormones

I'M OUT OF ESTROGEN...
And I HAVE A GUN

Any questions??
Total Testosterone Levels in Women Decrease With Age


$\rho = -0.54; P < 0.003$
Androgens in Women’s Health

- General well-being
  - Energy
  - Mood
- Increase libido and sexual satisfaction
- Bone physiology: increase bone mass
- Increase muscle mass
- Decrease hot flashes (may play a role)

Hormone Replacement in Women

- **Estrogen**
  - Compounded “bio-identical” creams
  - Synthetics (in Premarin, Prempro)
  - Patches, gels (bio-identical E2 available by prescription)

- **Progesterone**
  - Compounded “bio-identical” creams
  - Synthetics (in Premarin, Prempro)
  - Oral: Prometrium (available by prescription)

- **Testosterone**
  - Controversial
  - No FDA approved product available
  - Compounded “bio-identical” creams
  - Products for men
  - OTC DHEA
    - Precursor
“Can you give me something to make my hot flashes hotter? Hot enough to melt fat, burn calories and ignite passion!”
**For more information on aging in women:**

- **Websites:**
  - www.menopause.org
  - www.asrm.org
  - www.whi.org.
  - www.acog.org

- **Monographs**
  - [International Position Paper on Women's Health and Menopause: A Comprehensive Approach](http://www.nhlbi.nih.gov/health/prof/heart/other/menopaus/index.htm), to obtain pdf copy:

- **Books:**
  - The Hormone Survival Guide for Perimenopause, Nisha Jackson, PhD
  - The Sexy Years by Suzanne Somers
  - Dr. Susan Love's Menopause and Hormone Book: Making Informed Choices by Susan M. Love, Karen Lindsey
The Endocrinology of Aging: Can We Turn Back the Clock?

Issues for men
HORMONAL REGULATION: Male

- Hypothalamic - pituitary - gonadal axis

**Feedback**

Hypothalamus

GnRH

Pituitary

LH, FSH

Target organs (testes)

**Stimulation**

Steroids, Inhibin

Steroids (Testosterone)
1849: Discovery of Testosterone

“The testes act upon the blood, and the blood acts upon the whole organism.”

---A. Berthold, 1849

The beginnings of modern endocrinology…
Testosterone

- Steroid hormone
  - Diurnal variation with values highest between 6 - 9 AM
  - Predominately bound to SHBG; <1% free

- Synthesis
  - In males: by Leydig cells of testes under regulation by LH
  - In females: by adrenals, ovaries and metabolism of weak androgens in fat cells
Effects of Testosterone

- CNS ($\uparrow$ libido, energy)
- Larynx (lowers voice)
- Breast ($E_2 \uparrow$ size)
- Liver ($\downarrow$ SHBG, HDL)
- Kidney ($\uparrow$ EPO)
- Genitals ($\uparrow$ spermato-genesis, erections)
- Prostate ($\uparrow$ size, secr’ns)
- Skin ($\uparrow$ facial and body hair, sebum)
- Bone ($\uparrow$ BMD)
- Muscle ($\uparrow$ lean mass, strength)
- Adipose Tissue ($\downarrow$ abdominal fat)
- Immune system ($\downarrow$ autoimmunity)
- Blood ($\uparrow$ RBCs)
T Deficiency (<325 ng/dl) by Decade

Source: S. Harman, et al (BLSA); JCEM **86**: 724, 2001
Symptoms of Andropause

- Diminished sexual desire and erectile quality, particularly nocturnal erections
- Changes in mood with concomitant decreases in intellectual activity, spatial orientation ability, fatigue, depression and anger
- Decrease in lean body mass with associated diminution in muscle volume and strength
- Decrease in body hair and skin alterations
- Decrease in bone mineral density resulting in osteoporosis
- Increase in visceral fat
- In general, these symptoms reflect the decrease in testosterone
Key Clinical Features for Diagnosis

Endocrinologic Evaluation: A Partnership

- Clinical: astute, comprehensive clinical and investigative skills
- Laboratory: accurate, precise, sensitive and reliable measurement of circulating hormone levels
- Even with obvious, classical manifestations of endocrine disease, reliable laboratory studies are necessary to confirm the diagnosis
**Testosterone Forms in Serum**

- 68% is tightly bound to Sex Hormone Binding Globulin (SHBG)
- 30% loosely bound to albumin
- 2% free in the circulation
Measurement of Testosterone

- Total testosterone
- Free testosterone
- Bioavailable testosterone
- Calculations using Sex Hormone Binding Globulin (SHBG)
  - Free androgen index
  - Calculated free/bioavailable testosterone
Commonly Requested Lab Testing for Andropause

- Screening Test:
  - Total serum testosterone

- Confirmatory Tests:
  - Free testosterone and/or SHBG
  - LH and FSH (elevated with testicular dysfunction)
  - Semen analysis (if fertility is in question)
  - Prolactin (to rule out prolactinoma)

- Other assays
  - DHEA-S
  - Androstenedione

Testosterone Replacement

- Rationale/indications
  - Hypogonadal conditions:
    - Delayed puberty/failure of masculinization
    - Adult onset (Klinefelter’s, mumps, orchitis)
  - Andropause
    - Stabilizing or increasing bone density
    - Enhancing body composition by increasing muscle strength and reducing adipose
    - Improving energy and mood
    - Maintaining or restoring secondary sexual characteristics, libido and erectile function

- Regular follow-up is essential before initiating therapy and then every 3-6 months
  - Testosterone (total and free)
  - PSA
  - Hematocrit
Statistics & Trends

- Prescriptions for testosterone preparations have been increasing by 25-30% since 1993
- Number of men aged 65 in 2000 is 14,452,000
- Number of men aged 65 projected in 2030 is 31,343,000
For more information on the aging male:

- **Websites:**
  - [http://www.issam.ch/freetesto.htm](http://www.issam.ch/freetesto.htm)
  - [www.aua.org](http://www.aua.org)
  - [www.andropause.org.uk](http://www.andropause.org.uk)
  - [www.nia.nih.gov](http://www.nia.nih.gov)
  - [www.usrf.org](http://www.usrf.org)

- **Books:**
  - *Male Menopause* by Jed Diamond
  - *The Andropause Mystery: Unraveling Truths About the Male* by Robert S. Tan, Robert Tan (Paperback)
Is there a “fountain of youth”? 

- Optimization of endocrine functions
  - Reproductive hormone replacement for men and women
  - Growth Hormone support
  - Thyroid hormone replacement/support
  - DHEA-S/Adrenal support

All endocrine systems also affect and support
- Reducing inflammation
- Repair/re-growth
Bob Hope on aging:

“I’ll tell you how to stay young… hang around with older people”

Thank you!