

Hormone Replacement Therapy for Maintaining a Youthful Appearance

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Objectives

1. Review the effect of aging on the sex hormones (estrogen, progesterone, and testosterone) and the resulting effects on appearance.
2. Gain an understanding of the benefits of estrogen replacement in aging females to increase collagen and decrease wrinkling.
3. The advantages of topical progesterone in aging females. Is progesterone beneficial for skin firming and elasticity?
4. Explore the use of testosterone supplementation in andropause, also referred to as androgen deficiency in aging males (ADAM).

The effect of aging on estrogen¹

- Made in the ovaries, the corpus luteum, adrenal glands, and fat cells
- 3 types of estrogen molecules: estriol, estradiol, and estrone
- The ovaries stop regularly producing estrogen as we age
- The ↓ in estrogen leads to thinner skin, ↑ number and depth of wrinkles, and ↓ skin firmness and elasticity.

The effect of aging on progesterone¹

- Progesterone production is stimulated by the release of LH from the pituitary gland
- Precursor to sex hormones¹
- Maintains the uterine lining during pregnancy
- Enhances overall hormone balance after menopause
- Two types of progestogens:
 - Progesterone
 - Progestins: Synthetic progesterone²
 - MPA: structurally related to progesterone
 - Those related to testosterone, ie; norethindrone, norethindrone acetate norgestrel, and levonorgestrel

The effect of aging on testosterone

- 95% of the androgens are made in the testes, rest are made in the adrenals
- 98% of testosterone hormones are bound to SHBGs
- Sex hormone binding globulin (SHBG) ↑ with age^{3,4}
 - Bioavailable testosterone ↓ 2% per year
 - Total testosterone ↓ 1% annually after age 40⁵
 - Free testosterone concentrations ↓ by 2-3% with per year

Menopausal effects on wrinkles

- Aging is associated with skin wrinkling, dryness, & atrophy, due to decreased collagen and glycosaminoglycans (GAG's) content
 - Loss of connective tissue and GAG's of the dermis leads to increased skin rigidity and ↓ elasticity → wrinkling, dryness, atrophy⁶⁻⁸
 - Loss of skin tonicity → deepening of facial creases
- Approximately 30% of skin collagen is lost in the first five years after menopause⁹

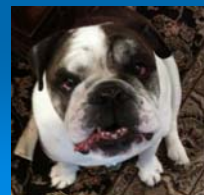
Estrogen's effects on wrinkles

- Results from NHANES* showed estrogen:
 - preserves skin collagen content
 - increases skin thickness
 - improves elasticity
 - limits the number and depth of wrinkles^{10,11}
- Estrogens can ↑ collagen + GAGs in the dermis which can ↓ skin wrinkling^{12,13}
- Postmenopausal women who were not taking HRT were significantly more likely to experience dry skin¹¹

* National Health and Nutrition Examination Survey

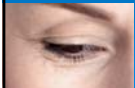
Estrogen replacement in post-menopausal females and its effects on wrinkles

- For women using estradiol gel or patches, increases in skin thickness were greatest over the first 6 months of treatment⁶
- Studies found an increase in skin thickness of 7-15% in postmenopausal women¹⁴



Estrogen replacement in post-menopausal females to decrease wrinkles

- After menopause women who received estrogen replacement therapy had:
 - ↑ skin collagen
 - ↑ thickness
 - When compared with age matched women who received no treatment^{16,17}
- Topical estrogen has been seen to ↑ collagen content, ↑ collagen synthesis, and thicken and increase elastic fibers of the dermis^{18,19}



Available Estrogen Products

- | | |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <ul style="list-style-type: none"> ❖ Synthetic estrogens <ul style="list-style-type: none"> • Pregnant horse urine estrogens • Molecularly different from human hormones ✓ Conjugated equine estrogen (Premarin®) ✓ Esterified estrogen ✓ Vaginal creams: Estropipate (Ogen®) | <ul style="list-style-type: none"> ❖ Bioidentical Hormones <ul style="list-style-type: none"> • Manufactured to be molecularly identical to hormones found in the body ✓ 17- Beta estradiol (Alora®, Climara®, Estrace®, Vivelle-Dot®, Estraderm®) ✓ Combinations with progesterone ✓ Compounded products |
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Topical progesterone for skin firming in post-menopausal females²⁰

- One study evaluated the use of a 2% progesterone cream on:
 - The elastic properties (number and depth of wrinkles, skin firmness) of the skin
 - Skin hydration and skin surface lipids were also measured
- The treatment group had continuous improvement in the 16 week study in regards to skin firmness, wrinkle count, and wrinkle depth)

Topical progesterone for skin firming in post-menopausal females

- The treatment group had a significant ↑ in skin firming
- Treatment group had greater wrinkle reduction (p>0.05)
- Wrinkles became more shallow and skin texture and elasticity improved
- Topical progesterone is well absorbed into circulation
- Topical progesterone could be an alternative to HRT for post menopausal women looking to improve skin appearance

Risks of estrogen/progesterone replacement therapy²

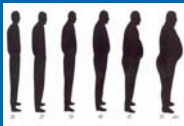
- Women's Health Initiative (WHI)
 - Study terminated after ~5 years
 - Oral estrogen-progesterone arm: 16,600 subjects
 - ↑ in:
 - ✓ Breast cancer
 - ✓ Risk of VTE events
 - ✓ Risk of ischemic stroke
 - ↓ risk of:
 - ✓ Colorectal cancer
 - ✓ Osteoporotic fractures
 - Neither protected or promoted CHD

Risks of estrogen/progesterone replacement therapy²

- Women's Health Initiative (WHI)
 - Estrogen only arm terminated:
 - 11,000 subjects
 - ↑ in stroke risk
 - Found a ↓ in hip fractures
 - No ↑ risk of coronary events or breast cancer

Andropause²¹

- AKA: Androgen Deficiency in Aging Males (ADAM)
- Clinical signs include:
 - ↓ In muscle mass and strength
 - ↓ In bone mass, osteoporosis,
 - ↑ In central body fat
- Symptoms include:
 - ↓ In libido and sexual desire, ED
 - ↓ Intellectual capacity (poor concentration, depression, fatigue)
 - Insomnia



Andropause^{22,23}

- Physical exam
- ADAM questionnaire
 - 10 questions regarding sexual performance, energy, mood, and strength
- Usual testosterone levels:
 - Total: 260-1000 ng/dL (< 300 ng/dL is considered low)
 - Bioavailable: 70-400 ng/dL
 - Free: 10-30 ng/L

Testosterone replacement in males

- Oral testosterone should not be used
 - Not readily bioavailable
 - Worsening LDL and HDL cholesterol
 - Potential liver toxicity^{24,25}
- Intramuscular injection
 - Cypionate and enanthate
 - Slow acting testosterone esters
 - Inject 50-400 mg every 2-4 weeks
 - Sustanon[®]

Testosterone replacement in males^{24,25}

- Transdermal
 - 24 hour continuous delivery
 - Produce daily circulating testosterone levels between 300-1000 ng/dL
 - ie. Androderm[®]: 2.5-7.5 mg applied once nightly, AndroGel[®] / Testim[®]: 5-10 g (delivers 5-10 mg/d) applied once daily
- Subdermal Implants
 - Longest duration of action with steady state lasting 4-7 months
 - Standard dose: 200 mg pellets (800 mg) implanted subdermally every 5-7 months²⁶
 - Testopel[®]

Testosterone replacement in males

- Buccal
 - Sustained release mucoadhesive buccal testosterone tablet
 - Applied to the upper gum region, 30 mg twice daily
 - Restores serum testosterone levels to physiological range within 4 hours^{27,28}
 - Striant®

"You can't help getting older, but you don't
have to get old"
George Burns

Benefits of testosterone therapy

- Improved sexual desire, function, and performance
- Increase bone mineral density
- Improve mood & energy
- Improve muscle mass & strength
- Improve cognitive function
- Improve quality of life¹⁹

Risks of testosterone therapy

- Worsen BPH
- Stimulate growth of prostate & breast cancer
- Cause liver toxicity & tumor
- Gynecomastia
- Testicular atrophy & infertility¹⁹

Conclusions

- Adequate studies have shown that topical estrogen is beneficial for improving the look of older skin
- Limited studies on the benefits of progesterone, however widely used
- WHI recommends:
 - Limit HRT use to the shortest duration
 - Best for treating menopause related symptoms
- Studies proved the beneficial effects of testosterone for improving the symptoms of andropause
- Personal decision to use hormone replacement, can be useful for improving patient quality of life

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Knowledge Assessment

- Following menopause, the thickness of skin and collagen content are increased in women on estrogen replacement therapy as compared to women not receiving treatment.
 - True
 - False
- Skin collagen increases at a more rapid rate in the initial postmenopausal years as compared with later years
 - True
 - False
- Andropause, or androgen deficiency in males, is characterized by: decreased sexual desire and erectile quality, depression and fatigue, decreased lean body mass, body hair and skin alterations, decreased bone mineral density, and increased visceral fat
 - True
 - False