

The biological rationale for estrogen therapy

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THE SCIENTIFIC BASIS FOR MEDICAL PRACTICE

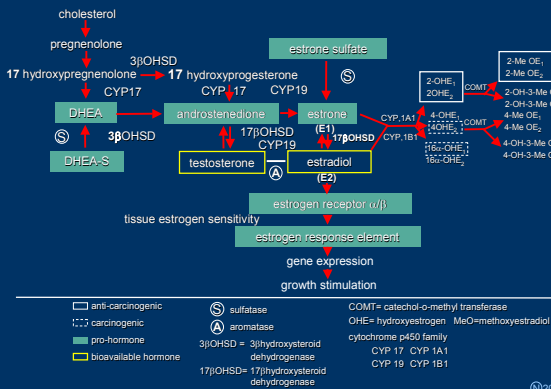
DATA SOURCE

Epidemiology
vs
Clinical trial evidence-based
vs
Biologic evidence-based

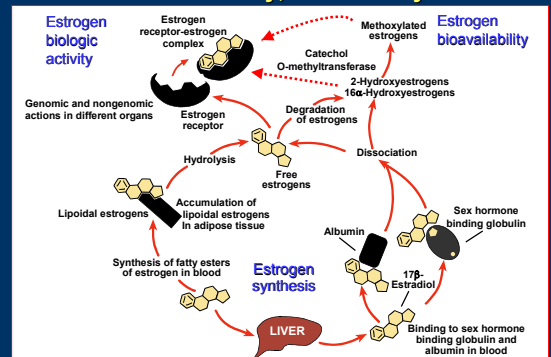
CLINICAL APPLICATION

Generic vs individualized

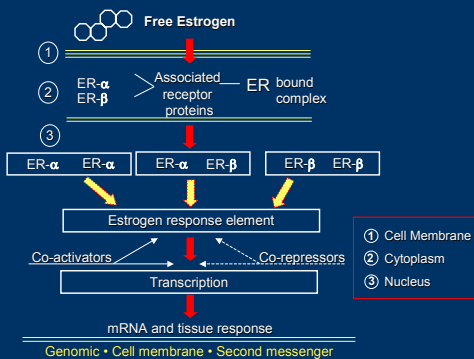
Synthesis and Metabolism of Estrogen



Postmenopausal Estrogen Synthesis, Bioavailability, and Activity



Estrogen Function

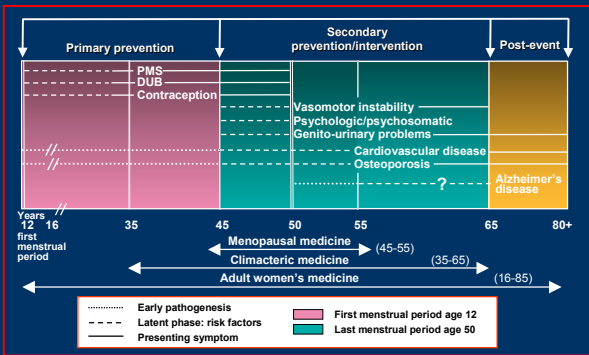


Clinical Message Menopause Generic • Biology Variable

- ▶ Estrogen receptor
 - ◊ Type
 - ◊ Distribution
 - ◊ Activity
- ▶ Estrogen synthesis and metabolism
 - ◊ CYP 450 genotype
 - ◊ Sulfatase activity
 - ◊ Aromatase activity
 - ◊ 17β-OH dehydrogenase activity
 - ◊ COMT activity
- ▶ Bioavailable estrogen/androgen
 - ◊ SHBG
 - ◊ "Hormone threshold"

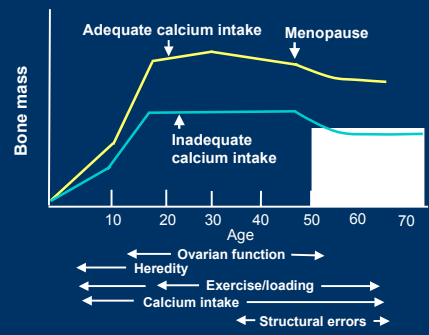
Presentation • Individual • HT response

The Climacteric and Menopause: "Window of Therapeutic Opportunity" for Hormone Therapy



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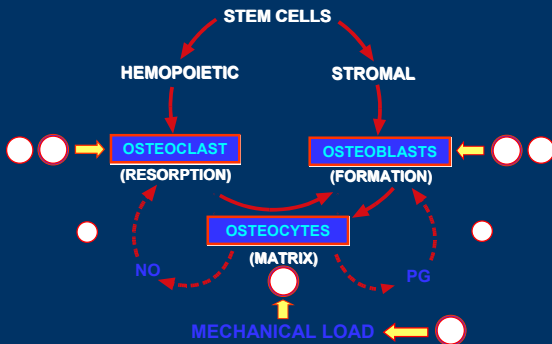
Schematic Representation of Bone Mass Accrual in Women



Heaney RP. Clin Obstet Gynecol. 1987;30:833-846.

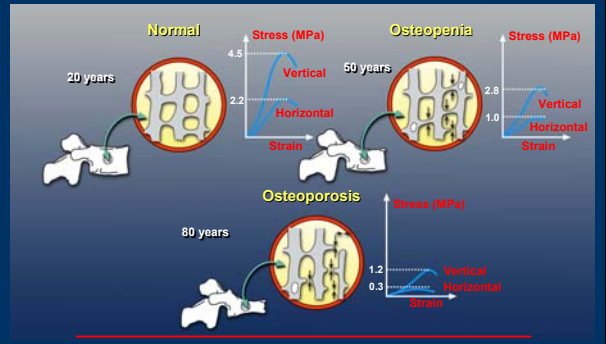
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Osteoporosis: Bone Remodeling, Sex Steroids, and Mechanical Loading



Notelovitz M. Fertil Steril. 2002;77(suppl 4):34-41. Adapted from Smit & Burger. JBMR 2000;15:301

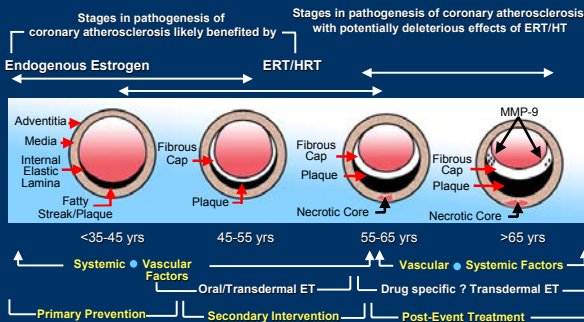
Changes in Trabecular Bone Structure and Biomechanical Competence with Age



Modified from Mosekilde L, et al. In: Takahashi HE, ed. Bone Morphometry. London, England: Nishimura/Smith Gordon, Niigata, 1990:367-370.

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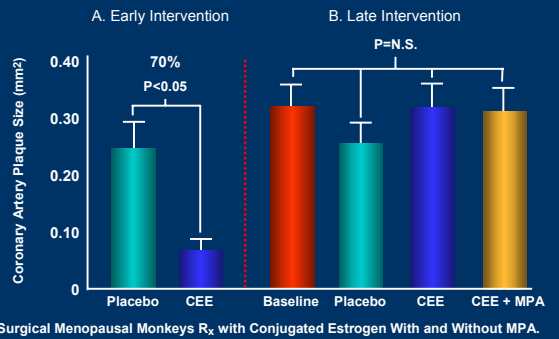
Cardiovascular Disease and Hormone Therapy



Modified from Clarkson, 2000.

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Hormone Therapy and Plaque Reduction

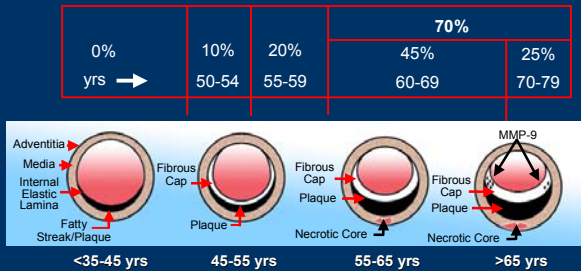


Surgical Menopausal Monkeys Rx with Conjugated Estrogen With and Without MPA.

Clarkson 2002. INT. J. FERTIL. 47:61

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Relation of Age Distribution in WHI* to Stage of Progression of Coronary Artery Atherosclerosis



* = Women's Health Initiative

Clarkson, 2002

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Pharmacologic Modulation of Estrogen Activity

Modifiable

- ▶ Free E₂, SHBG
 - ◊ Route of ET
 - ◊ Type of ET
 - ◊ Androgen Co-Rx
- ▶ Estrogen receptor activity
 - ◊ SERMs
- ▶ Estrogen metabolism
 - ◊ Inhibitors of
 - Sulfatase
 - Aromatase

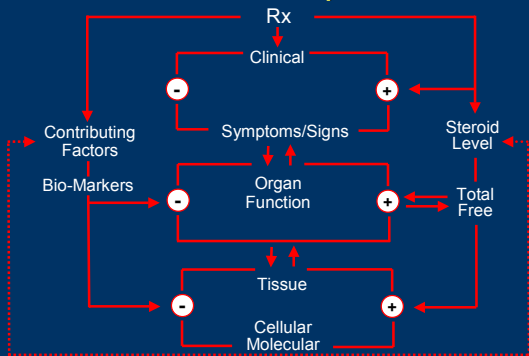


Non-modifiable

- ▶ Genotype
 - ◊ α/β
 - ◊ Homodimer
 - ◊ Heterodimer
- ▶ Tissue ER distribution
- ▶ CYP 450 genotype
 - ◊ E synthesis
 - ◊ E metabolism

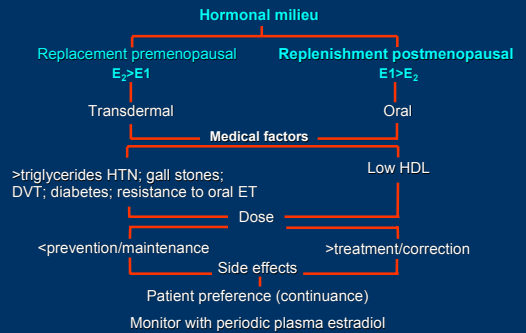
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Evaluating Hormone Therapy: Function and Bioequivalence



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Estrogen Therapy: Selecting Route and Dose



Notelovitz M, 1998

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