WEIGHT GAIN DURING MENOPAUSE—EMERGING RESEARCH
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MENOPAUSE — WHEN DOES IT OCCUR?
• The cessation of the menstrual cycle for one year.
• Age range for menopause (last period from natural causes) is between 40 and 61.
• The average age for the last period is 51 years.
• Age differs significantly around the world
  • India and Philippines – 44 years of age

STAGES OF MENOPAUSE: WHO AND INTERNATIONAL MENOPAUSE SOCIETY
• Pre-menopause
  • The entire reproductive period up to the final menstrual period
• Perimenopause
  • Period immediate prior to the menopause (and the first year after menopause)
• Menopause
  • Natural menopause is recognized to have occurred after 12 consecutive months of amenorrhea, for which there is no other obvious pathological or physiological cause.
• Postmenopause
  • The period of time after the final menstrual period, regardless of whether the menopause was induced or spontaneous

PHASES OF THE MENSTRUAL CYCLE
• Menstrual phase
• Follicular phase
• Ovulation phase
• Luteal phase
HOW DOES THIS CHANGE DURING MENOPAUSE?

- Perimenopause:
  - Endocrinological, biological, and clinical features of approaching menopause commence
- Major hormonal changes:
  - Erratically higher estradiol levels
  - Decreased progesterone levels
  - Disturbed ovarian-pituitary-hypothalamic feedback relationships

ESTROGEN ↑ PROGESTERONE ↓

HYPOTHALAMIC – PITUITARY – OVARIAN FEEDBACK

- The primary hormonal changes of perimenopause result not only from the "aging ovary" but also from the disruption of the usual positive and negative hormonal and paracrine feedback (cell to cell communication) networks controlling the normal ovulatory menstrual cycle

INHIBIN AND CONTROL OF PERIMENOPAUSAL FOLLICLE STIMULATING HORMONE

- Higher estradiol levels normally act to suppress rising FSH levels, however during perimenopause this feedback fails – particularly at the follicular-luteal transition
- At the point in which each ovary holds fewer that 100 follicle, Inhibin B levels decline and no longer hold early cycle FSH level in check
- Elevated FSH, in turn, appears to stimulate the second estradiol peak called LOOP during the luteal phase
WHAT ABOUT TESTOSTERONE?

- Levels peak in a woman’s 20s and decline slowly thereafter.
- By menopause, level is at half of its peak.
- Ovaries continue to make testosterone even after estrogen production stops.
- Testosterone production from adrenal glands also declines with aging but continues after menopause.

WHY IS THERE AN INCREASE IN WEIGHT DURING THE MENOPAUSE TRANSITION?

- Because the menopause transition happens over a number of years, it is difficult to determine whether the increased propensity for weight gain at midlife is primarily a consequence of the menopause transition or of advancing age.
- Age → decrease in energy expenditure
- Menopause → changes in the hormonal environment
- Most likely a combination of both!

AGE VERSUS MENOPAUSE

- Followed premenopausal women for four years
  - FSH increased over four years in all groups
  - Weight increased in all groups following four years but only significant in postmenopausal group
  - SAT increased in all groups
  - Estradiol decreased in postmenopausal group
  - EE decreased by half in postmenopausal group
  - VAT increased in postmenopausal women

SO WHAT DO ALL THESE HORMONAL CHANGES MEAN IN REGARDS TO WEIGHT GAIN?

90% of women approaching menopause gain extra pounds

A woman’s age-related weight gain occurs around her stomach due to hormonal changes.
**WHAT DO WE CURRENTLY KNOW?**

- Increase in body weight
- Increase in total body fat
- Increase in central adiposity
- Increase in weight/fat = increase in heart disease and certain cancers such as breast cancer

- Even in weight stable post menopausal women there is a progressive change in body composition:
  - Loss of lean tissue in the legs
  - Gain in fat tissue in the trunk

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**RESEARCH SHOWS….**

- 38 premenopausal women followed for 6 years

- Experienced menopause (1/2 the subjects):
  - Lost more fat free mass
  - Greater decreases in resting metabolic rate
  - Increases in fat mass
  - Increases in fasting insulin levels
  - Increases in waist to hip ratio
  - Less physical activity

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**RESEARCH SHOWS…….**

- Women who are more active have lower levels of body fat and abdominal fat and are less likely to gain total and abdominal fat during menopause than those with low levels of activity

- Prevalence of abdominal obesity is almost double that of general obesity
  - 65.5% in women 40-59 years
  - 73.8% in women aged 60 years and over

- Substantial evidence that perimenopause is associated with a more rapid increase in fat mass and a redistribution of fat to the abdomen
AGE PROMOTES WEIGHT GAIN
- Loss of muscle mass
- Decline in maximal aerobic power

More time must be spent to equal same amount of energy expenditure

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IS WEIGHT GAIN HORMONAL?
- Estrogens and xenoestrogens (hormones that imitate estrogen) exert a great variety of actions in almost every cell type and through diverse cellular and molecular pathways

ESTROGEN DEFICIENCY AND WEIGHT GAIN
- Animal studies shows multiple mechanisms that cause weight gain with estrogen deficiency:
  - Increased food intake
  - Decreased spontaneous physical activity
  - Suppression of the metabolic rate

ESTROGEN AND ESTROGEN RECEPTORS
- In humans 17β-estradiol (E2) is the most potent estrogen followed by estrone (E1) and estriol (E3)
- We also have estrogen receptors: ERα and ERβ
- Most of the know effects of estrogen have been shown to be mediated via a direct interaction of estrogen with ERs, ERα and ERβ
**ESTROGEN RECEPTORS**

- The classical estrogen receptor ERα appears to be a major regulator of adipose tissue but recent research has also indicated a possible role for the more recently discovered estrogen receptor, Erβ.

**ESTROGEN AND CENTRAL EFFECTS**

- Estrogens may regulate fat tissue mass by central and/or peripheral effects.
  - Central effects are mediated via the CNS and include regulation of food intake and physical activity.
  - The main regulatory site is the hypothalamus.

**ESTROGEN AND CENTRAL EFFECTS**

- Estrogen has a negative effect of feeding through actions on the hypothalamus.
  - In the brain (mice) the disruption of ERα in the hypothalamus leads to weight gain, increased visceral adiposity, hyperplagia, hyperglycemia and impaired energy expenditure.

**ESTROGEN AND PERIPHERAL EFFECTS**

- ERα levels are reduced in adipocytes from obese compared to normal weight females supporting a role of ERα signaling in the control of body weight.
  - Estrogen can directly inhibit adipose deposition by decreasing lipogenesis. This action happens by decreasing the activity of lipoprotein lipase an enzyme the regulates lipid uptake by adipocytes.
ESTROGEN AND PERIPHERAL EFFECTS

- The increases in adipose mass in women results from increases in adipocyte number and size
  - Adipocyte number in the gluteal subcutaneous fat was increased by 34% in girls compared to boys at adolescence
  - Adipocyte size was also increased 45% compared to similar-aged boys

- This receptor (ERα) is related to glucose metabolism in different tissue including skeletal muscle, adipose tissue, liver, brain and endocrine pancreas
  - GLUT4 is the major insulin-stimulated glucose transporter and the main rate limiting step in insulin-stimulated glucose uptake in skeletal muscle and adipocytes
  - GLUT4 expression in the skeletal muscle membrane depends upon ERα. It is reduced in ERα knockout mice.

ESTROGEN AND LEPTIN

- Leptin decreases food intake and increases EE
  - Kastin et al (2001) found that a chronic loss of ovarian function decreased the transport of leptin into the brain of mice
  - This has contributed to the hypothesis that obesity results from a defect in system shown to transport intact leptin into brain parenchyma

ESTROGEN THERAPY

- Effects of estrogen therapy in postmenopausal women show a reduction in central adiposity
  - ERT has a protective effect against obesity however the increase CV and cancer risks associated with HRT make estrogen replacement itself an unsuitable option
SUMMARY OF ESTROGEN EFFECTS ON ADIPOSE TISSUE

Direct effects

- Lipogenesis
  - Decrease lipoprotein lipase
- Lipolysis
  - Increase hormone sensitive lipase activity
  - Increase epinephrine induced lipolysis
  - Site specificity attenuated subcutaneous tissue lipolysis

Central Effects

- CNS/hypothalamus effect
  - Decrease feed consumption
  - Decrease leptin secretion
  - Increase activity and energy expenditure

EXERCISE RECOMMENDATIONS

- Physical activity may not entirely prevent weight gain with age but it may protect against the development of obesity and disease.

- Post menopausal women decreased their leisure time physical activity and had a slightly lower resting metabolic rate compared with baseline suggesting a positive energy balance of almost 300 kcal/day which could lead to substantial weight gain over time.

HOW SHOULD WE DESIGN AN EXERCISE PROGRAM?

- Most research focuses on low to moderate intensity activity with success

WHAT ABOUT HIGH INTENSITY ACTIVITY?

- Menopause
  - Increase in FSH
  - Unbalanced Estrogen (Estriol) and Progesterone Levels
- Leaving excess cortisol in system
  - Lack of Estriol cannot produce enough CRG or transcortisol, the protein that binds to cortisol.
  - Stress occurs in unbalanced system producing cortisol

- Cortisol
  - Blood volume
  - Food intake
  - Protein degradation in muscle & fat
- We must perform exercise that doesn’t exacerbate cortisol in the system.