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Menopause: Biomarkers and Physiological Changes

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Abstract

An expected 1.1 billion women will be considered postmenopausal by the year 2025.[1] The inevitable physiological phenomenon of menopause can be unpleasant and intolerable for some women. Fortunately, there are actions and interventions that can help minimize its adverse effects.

Alterations in hormone levels can contribute to disruptive symptoms including vasomotor changes, hot flashes, headaches, poor sleep, depression, and weight gain. Biochemical and physiological changes occur as well and can include dyslipidemia and impaired glucose tolerance.

Hormone levels can be monitored during the perimenopausal period to help identify the stages of menopause, including estrogen, progesterone, testosterone, AMH, FSH, LH, and DHEA.

Biomarkers of chronic disease should also be assessed in perimenopause due to an associated increased risk of cardiovascular and metabolic disorders. Trends toward dysfunction should be identified and addressed early in order to practice prevention instead of deflection.

Introduction

Menopause is actually a full stop, not a pause.

It is the cessation of menstruation in women that can occur at 40 to 60 years of age, though it usually occurs between 45 and 52. More than 80% of women will experience disruptive symptoms that can last for 15 years or more.[2]

Menopause itself reflects a change in complex interactions involving the ovarian, pituitary, and hypothalamic hormones that regulate cyclic menstruation.[3] A women can no longer become pregnant once menopause has occurred.

Menstrual irregularities can begin within 2-10 years of menopause in a phase called perimenopause. Alterations in the cyclical nature of circulating hormones, releasing hormones, and peptides facilitate "the change." The reduction in hormone production at this time may increase the ratio of estrogen to progesterone which can increase risk of uterine cancer.[4] Melatonin levels were also found to decline from premenopause to postmenopause.[5] [6]

Symptoms of menopause may be mild for some but intolerable for others. Lifestyle changes and natural approaches may resolve menopausal symptoms. However, for some women, hormone replacement therapy may be advised.

This review will cover

- ✓ The Biology and Physiology of Menopause
- ✓ Phases of Menopause
- ✓ Estrogen and Progesterone Functions
- ✓ Chronic Diseases Associated with Menopause
- ✓ Identifying Menopause
- ✓ Laboratory Evaluation of Menopause
- ✓ Evaluation of Cardiac Risk in Menopause
- ✓ Lipid Changes in Menopause
- ✓ Additional Testing
- ✓ Natural Approaches to Menopause
- ✓ Hormone Replacement Therapy
- ✓ Optimal Takeaways

Biology and Physiology of Menopause

Menopause occurs once ovaries become depleted of oocytes (immature eggs) and the cyclical pattern of hormones and peptides ceases. The significant decrease in estrogen, especially estradiol, can contribute to unpleasant symptoms and physiological consequences. Decreased progesterone also contributes to symptomatology.

Although ovarian production of steroid hormones declines after menopause, estrogens can still be produced elsewhere including adipose tissue, and higher estrogen levels can be seen in obesity. Steroid hormones can also be produced from dehydroepiandrosterone (DHEA) in significant amounts in a process called intracrinology.[7]

However, as the use of LDL cholesterol for estrogen production in the ovaries decreases, circulating LDL cholesterol increases, characterizing the dyslipidemia associated with menopause.[8] Within one year of menopause, total and LDL-cholesterol and apolipoprotein B can become substantially elevated.[9]

Menopause can occur at an earlier than expected age due to a phenomenon known as premature ovarian failure (POF). Researchers note that POF can be triggered by[10]

- ✓ Chromosomal disorders, e.g., Fragile X syndrome, Turner syndrome
- ✓ Eating disorders
- ✓ Environmental pollution
- ✓ Excessive exercise
- ✓ Genetic disorders
- ✓ Medications for fibroids or endometriosis
- ✓ Obesity
- ✓ Stress

Early menopause may also be brought on by removal of both ovaries (bilateral oophorectomy), radiation, chemotherapy, or analogues of gonadotrophin-releasing hormones.[11]

The age at which menopause occurs is influenced by[12]

- ✓ Alcohol use
- ✓ Diet
- ✓ Eating disorders
- ✓ Education
- ✓ Employment
- ✓ Ethnicity
- ✓ Exposure to endocrine disrupting chemicals
- ✓ Oral contraceptive use
- ✓ Physical activity
- ✓ Smoking
- ✓ Weight

Menopause occurs in phases

Initial observations include:[13]

✓ Premenopause:	No cycle changes, menses occurred within 3 months
✓ Early perimenopause:	Less predictable cycles, menses within last 3 months
✓ Late perimenopause:	No menses for 3-11 months
✓ Postmenopause:	12 consecutive months of amenorrhea (no menses)
✓ Early postmenopause:	24 or fewer months since date of final menstruation
✓ Late postmenopause:	Greater than 24 months since final menstruation

The 2011 update to WHO Stages of Reproductive Aging workshop known as STRAW +10 further defines stages and characteristics of menopause for women over age 40.[14]

Perimenopause (menopausal transition and early postmenopause):

- ✓ Early menopausal transition:
  - 7 or greater day difference in length of consecutive cycles
  - Variable duration
- ✓ Late menopausal transition:
  - Intervals of no menses (amenorrhea) 60 or more days per interval
  - May last 1-3 years

Postmenopause

- ✓ Early postmenopause
  - 2-6 years
- ✓ Late postmenopause
  - Remaining lifespan

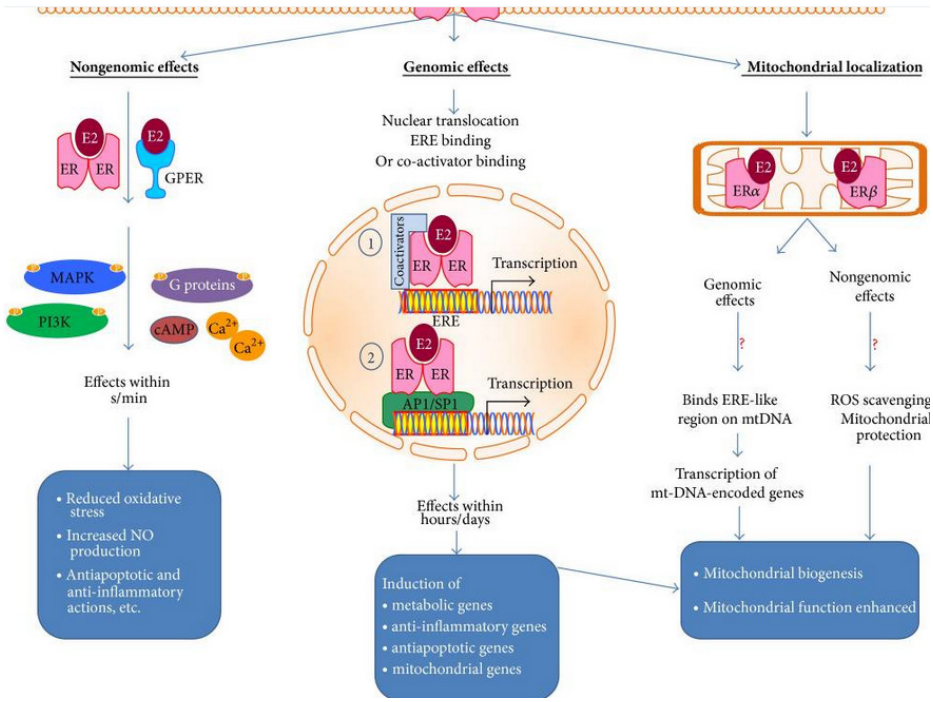
Estrogen and Progesterone

There are four types of estrogen: estrone (E1), estradiol (E2), estriol (E3), and estetrol (E4), with estradiol being the most abundant and the most potent. When ovarian production of estradiol decreases with menopause, other tissues are able to synthesize it, including adipose tissue, bone, brain, and smooth muscle cells of the vascular endothelium.[15] In fact, estrogen receptors are found in non-reproductive tissues including adipose tissue, liver, skeletal muscle, and the central nervous system, highlighting its importance in metabolism.[16]

Several functions in the body are regulated by estrogen and progesterone and these functions will be affected when circulating hormone levels fluctuate:[17] [18] [19]

Estrogens regulate	Progesterone regulates
✓ Cardiovascular system	✓ Brain
✓ Cortisol release during stress	✓ Ovary
✓ Energy regulation	✓ Uterine
✓ Food intake regulation	✓ Mammary gland function
✓ Glucose homeostasis	
✓ Insulin action	
✓ Lipid homeostasis	
✓ Mitochondrial function	
✓ Neurologic system	
✓ Skeletal system	
✓ Vascular system	

Mechanisms of Estrogen Action



Gupte, Anisha A et al. "Estrogen: an emerging regulator of insulin action and mitochondrial function." Journal of diabetes research vol. 2015 (2015): 916585. doi:10.1155/2015/916585 [R] This is an open access article distributed under the Creative Commons Attribution License.

Increased Risk of Disease Associated with Menopause

The relative deficiency of estradiol brought on by menopause triggers detrimental changes including dyslipidemia, decreased metabolic rate, increased central adiposity, and metabolic syndrome. These underlying physiological shifts can progress to more severe disease including type 2 diabetes, cardiovascular disease, and non-alcoholic fatty liver disease (NAFLD).[20]

Mitochondrial dysfunction also occurs in association with decreased circulating estrogen. This dysfunction leads to a decrease in lipid oxidation, increase in lipid storage, and the increased adiposity seen with menopause.[21]

A significant portion of a woman's life may be spent in menopause. A primary objective should be to reduce risk of chronic disease and optimize health during this period. Preventative steps should be taken to address the most common disorders of concern including:[22] [23] [24] [25] [26] [27]

- ✓ Cancer
- ✓ Cardiovascular disease
- ✓ Chronic obstructive pulmonary disease
- ✓ Cognitive decline
- ✓ Dementia
- ✓ Depression
- ✓ Diabetes mellitus
- ✓ Endothelial dysfunction
- ✓ Hormone-related cancers (e.g., breast and endometrial)
- ✓ Hypertension
- ✓ Metabolic syndrome
- ✓ Migraine
- ✓ Musculoskeletal disorders
- ✓ NAFLD
- ✓ Obesity
- ✓ Osteoarthritis
- ✓ Osteoporosis
- ✓ Sleep disturbances
- ✓ Vasomotor symptoms

Identifying Menopause

Some women glide through menopause without disruptive symptoms while some experience unbearable discomfort that needs to be addressed.

For many women, changes in mood and sleep patterns characterize the perimenopausal period and can extend throughout menopause. The transition from pre-to postmenopause can take up to four years.[28]

Approximately 80% of women transitioning into menopause will have symptoms though not all will seek intervention. The most disruptive appear to be vasomotor symptoms such as night sweats, hot flashes, and sleep disruption.[29] Researchers suggest that menopausal vasomotor symptoms may reflect adverse vascular changes. Therefore, risk of endothelial dysfunction should be assessed as well.[30]

Signs and Symptoms of Perimenopause and Menopause[31] [32] [33] [34] [35] [36] [37] [38] [39] [40] [41]

Physiological

- ✓ Back pain
- ✓ Bone density loss, bone pain
- ✓ Cognitive decline
- ✓ Decreased libido, decreased sexual function
- ✓ Dental caries
- ✓ Depression
- ✓ Difficulty concentrating
- ✓ Dry mouth/ xerostomia, burning mouth
- ✓ Elevated heart rate
- ✓ Emotional distress
- ✓ Genitourinary syndrome of menopause (GSM)
- ✓ Headaches
- ✓ Gingival atrophy
- ✓ Jawbone osteoporosis
- ✓ Joint pain, aches, or stiffness
- ✓ Loss of lean body mass
- ✓ Mood changes, mood swings
- ✓ Osteopenia, osteoporosis
- ✓ Palpitations
- ✓ Periodontitis
- ✓ Psychological distress
- ✓ Sarcopenia
- ✓ Sexual dysfunction
- ✓ Skin lesions
- ✓ Sleep disruption, insomnia
- ✓ Taste changes
- ✓ Vaginal dryness, discharge, itchiness or irritation
- ✓ Vasomotor (hot flashes/ flushes, night sweats)
- ✓ Visceral and abdominal adiposity
- ✓ Weight gain, obesity

Biochemical

- ✓ Dyslipidemia
- ✓ Glucose intolerance
- ✓ Hyperinsulinemia, insulin resistance
- ✓ Inflammation
- ✓ Decreased estradiol, progesterone, AMH, adiponectin, HDL-C
- ✓ Increased triglycerides, total cholesterol, LDL, VLDL, FSH, leptin, proinflammatory markers

The Menopause Rating Scales (MRS) is a validated tool for assessing menopause-related symptoms categorized as:[42]

Somatic	Psychological	Urogenital, sexual
Cardiac discomfort	Anxiety	Bladder issues
Hot flashes	Depressed mood	Vaginal dryness
Joint issues	Exhaustion, physical & mental	
Muscle issues	Irritability	
Sleep issues		

Vasomotor Symptoms

Vasomotor symptoms occur in 80% of perimenopausal women and are the most common complaints that drive a woman to seek intervention and relief.[43] Although hormone replacement therapy may be the most effective at relieving these symptoms, it may be contraindicated in some women (e.g., breast cancer survivors), or rejected by others due to potential adverse health effects. A trial period of 2-4 weeks of non-hormonal intervention will indicate if a non-hormonal approach is efficacious.[44]

Hot flashes/flushes appear to occur due to an abrupt decrease in serum estrogen, fluctuations in neurotransmitters such as serotonin and norepinephrine, and peptides neurokinin-B and calcitonin gene-related peptide.[45]

Headache

The hormonal changes associated with menopause may trigger headaches or even migraines in some individuals. Unfortunately, for individuals with a history of headaches or migraine, menopause may make symptoms worse.

A 2018 review notes that for individuals with aura-associated migraines, hormone replacement therapy may increase ischemic stroke risk and may be contraindicated. Other non-hormonal therapies may provide some relief, including black cohosh, vitamin E, acupuncture, yoga, and aerobic exercise.[46] If estrogen therapy is used for migraine without aura, transdermal delivery is recommended.[47]

Laboratory Evaluation of Menopause

Research suggests that severity of some symptoms is associated with variability of hormone levels, not just general declines.[48] [49]

Hormonal fluctuations during the perimenopausal period cause irregular menstruation, hot flashes, sleep disruption, and changes to vaginal integrity. Laboratory testing can help confirm that these symptoms are related to menopausal changes, especially in women younger than 50 or those who have had a hysterectomy.[50]

For women with vasomotor symptoms whose menstruation has ceased for greater than one year, diagnosis of menopause can be fairly straightforward without the need for extensive laboratory investigation.[51]

However, the perimenopausal period is characterized by notable biomarker patterns that can be assessed. During the transition from pre- to postmenopause, serum levels of estrone (E1), estradiol (E2), and sex hormone binding globulin (SHBG) decrease while levels of Follicle Stimulating Hormone (FSH) and Luteinizing Hormone (LH) increase.[52] Progesterone will decline as well.[53]

These changes have biochemical causes and effects:[54]

- ✓ Serum estrogens and inhibins decrease as ovarian follicles are depleted.
- ✓ Increases in pituitary gonadotrophins FSH and LH occur in the body's attempt to stimulate ovulation.
- ✓ Depletion of estrogen and progesterone contribute to other biochemical changes in the body as well.

Serum concentrations of DHEAS follow a unique pattern in menopausal women with levels declining with age until early menopause, with an increase between early and late menopause. After this period, levels of DHEAS begin to decline again.[55]

Other biochemical changes can be detected as well due to the glucose intolerance, hyperinsulinemia, insulin resistance, and dyslipidemia that commonly occurs with menopause. These metabolic changes can progress to coronary and peripheral artery disease.[56]

Salivary and urine measurement of hormone metabolites may be employed during the assessment of menopause. However, such evaluation is outside the scope of this review.[57] [58]

Laboratory Changes Associated with Menopause[59 60 61 62 63]

Decreased

- ✓ Adiponectin
- ✓ AMH
- ✓ Estradiol
- ✓ Ghrelin
- ✓ HDL-cholesterol
- ✓ Inhibin A and B
- ✓ Progesterone

Increased

- ✓ Apolipoprotein B
- ✓ Cholesterol, total and LDL
- ✓ FSH
- ✓ Leptin
- ✓ LH
- ✓ Resistin
- ✓ Triglycerides

Biochemical Phases of Menopause

Although not necessarily diagnostic, distinct changes in hormone levels can be observed during various phases of menopause:[64 65]

Perimenopause

- ✓ Early menopausal transition
  - Disturbed regulation of ovulation
  - Elevated FSH, low anti-mullerian hormone, low inhibin B, minor increase in LH
  - Progesterone and estradiol tend to be unaffected in this phase unless superimposed ovulatory LOOP cycles persist, leading to highly variable estradiol levels and low luteal phase progesterone.
- ✓ Late menopausal transition
  - Paucity of ovulation
  - FSH above 25 IU/L, Low AMH (may be undetectable), low inhibin B
  - LDL and triglycerides can increase between early perimenopause and early postmenopause.
- ✓ Early menopause
  - Elevated variable FSH, low AMH, low inhibin B
  - Bone mineral density loss is greatest the year before menstruation ceases and for two years after with annual losses of 1.8-2.3% in the lumbar spine and 1-1.4% in the hip. Bone loss was 35-55% greater in women in the lowest tertile of body weight.
  - Researchers suggest that bone loss in perimenopause may be due to elevated FSH, cortisol, and epinephrine instead of reductions in estradiol.

Menopause

- ✓ Elevated stable FSH, very low AMH, very low inhibin B
- ✓ Estrogen and progesterone are both low
- ✓ Estrone higher than estradiol

Postmenopause

According to the Association for Clinical Biochemistry & Laboratory Medicine, the following serum hormone levels are characteristic of the postmenopausal period:[66]

	Premenopausal	Postmenopausal
Anti-mullerian Hormone (AMH)	Greater than 2.8 ng/mL 20 pmol/L	Below 2.1 ng/mL 15 pmol/L
Estradiol	Depends on point in cycle	2.7-7.4 pg/mL 9.8-27.1 pmol/L
FSH	10 IU/L	Above 60 IU Mean 100 IU/L
Inhibin A	25 ng/L	10 ng/L or less
Inhibin B	50 ng/L	25 ng/L or less
LH	Depends on point in cycle	10-45 IU/L
Testosterone, total	11.82-26.8 ng/dL 0.41-0.93 nmol/L	13.26-30.26 ng/dL 0.46-1.05 nmol/L
Testosterone, free	1.6-3.9 pg/mL 5.5-13.4 nmol/L	1.5-4.2 pg/mL 5.4-14.7 pmol/L

The following reference intervals represent ranges for estradiol and progesterone used by commercial labs. As you can see values vary from timing of the blood draw but also vary from lab to lab. That is why it's important to use the same laboratory to repeat and compare lab values.

Standard Reference Intervals	Quest Diagnostics[67] [68]	Labcorp[69] [70]
Serum **Estradiol pg/mL**	Female: Follicular Phase 19-144 Mid-Cycle 64-357 Luteal Phase 56-214 Postmenopausal ≤31 Male ≤39	Adult female: Follicular: 12.5–166 Ovulation: 85.8–498 Luteal: 43.8–211 Postmenopausal: <6.0–54.7 Adult male: 7.6–42.6
Serum **Progesterone ng/mL**	Adult Females Pre-Menopausal Mid Follicular ≤0.3 Pre-Menopausal Surge 0.1-1.5 Pre-Menopausal Mid Luteal 6.7-22.2 Postmenopausal Phase ≤0.2 Adult Males over 30 ≤0.2	Female Follicular phase 0.1–0.9 Luteal phase 1.8–23.9 Ovulatory phase 0.1–12.0 Postmenopausal 0.0–0.1 Male 0.0–0.5

Cardiovascular Risk in Menopause

The relationship between sex hormones and CVD risk is not entirely clear and research is ongoing. Data from 2834 postmenopausal women in the Multi-Ethnic Study of Atherosclerosis (MESA) were evaluated for their association with heart disease.[71]

- ✓ Results indicate elevated testosterone (T) and an increased ratio of testosterone to estradiol (E2) were associated with increased risk of cardiovascular disease and heart failure.
- ✓ However, the relationship between T/E2 ratio and heart failure was U-shaped, demonstrating increased risk when the ratio was extremely high or extremely low.
- ✓ Higher levels of estradiol correlated with reduced risk of heart disease and both estradiol and DHEA had an inverse association with risk of heart failure.
- ✓ Statistically significant differences in biomarkers at baseline included:

MESA **Postmenopause hormones & CVD risk**	**No CVD**	**CVD**
Estradiol pg/mL pmol/L	 19.9 73	 17.9 66
DHEA ng/mL nmol/L	 2.97 10.31	 2.68 9.3
Bioavailable T ng/dL nmol/L	 6.05 0.21	 6.92 0.24
Total T to E2 ratio T/E2	 11.55	 15.42
CRP mg/L	 2.5	 3.2
D-dimer ug/mL nmol/L	 0.2 1.1	 0.3 1.64
Fibrinogen mg/dL	 354	 371
IL-6 pg/mL	 1.3	 1.6
HDL cholesterol mg/dL mmol/L	 57 1.48	 54 1.4
Exercise **MET-min/week**	 3630	 2925
eGFR	75.8	71.5
Waist-to-hip ratio	0.91	0.94
BMI	28.5	29.6
Systolic and diastolic blood pressure	128.4 mm Hg 68.9 mm Hg	139.7 mm Hg 70.3 mm Hg

The following biomarker changes, provided by the Association for Clinical Biochemistry & Laboratory Medicine, reflect the dyslipidemia and increased cardiovascular risk associated with menopause.[72]

Cardiovascular Biomarker Patterns in Menopause	Premenopausal	Postmenopausal
Total cholesterol mg/dL mmol/L	 153.4 3.97	 211.2 5.47
Triglycerides mg/dL mmol/L	 101.1 1.14	 125.5 1.42
HDL mg/dL mmol/L	 46.7 1.2	 27.7 0.7
VLDL mg/dL	 20.1	 25.1
LDL mg/dL mmol/L	 85.6 2.2	 158.4 4.1
ADMA umol/L	 0.4	 0.82 (non-obese) 1.34 (obese)
CRP mg/L	 2.1	 3.8

A large retrospective observational study of 275 menopausal women, conducted at the Hospital Quiron Salud in Madrid, found significant differences in several metabolic biomarkers during the transition between perimenopause and postmenopause:[73]

Biomarker	Perimenopause	Postmenopause
Total cholesterol mg/dl mmol/L	 205 5.3	 214 5.5
LDL-C mg/dL mmol/L	 122.7 3.2	 134 3.5
HDL-C mg/dL mmol/L	 66 1.7	 62 1.6
Triglycerides mg/dL mmol/L	 76 0.86	 87.5 0.99
Fasting glucose mg/dL mmol/L	 92 5.11	 96 5.33
Uric acid mg/dL mmol/L	 4.3 0.26	 4.6 0.27
Calcium mg/L mmol/L	 94 23.5	 95 23.8
Vitamin D 25(OH) ng/mL nmol/L	 25.8 64.4	 28.6 71.4
TSH mIU/L	1.3	1.7

Lipids

Hormonal changes that occur during the menopausal transition appear to trigger dysregulation of lipid metabolism including alterations in circulating lipoproteins and triglycerides, and decreased beta oxidation of fatty acids. Combined with excess adipose tissue, these changes contribute to increased synthesis of adipocytokines, proinflammatory cytokines, reactive oxygen species, lipid peroxidation, insulin resistance, and ultimately CVD and type 2 diabetes if not addressed effectively.[74]

Adiposity itself is associated with cardiovascular risk. Total fat mass appears to directly affect circulating estrogen, which is relatively higher in obese versus non-obese menopausal women. Though estradiol in general is considered to be cardioprotective, higher levels in conjunction with obesity may reflect increased CVD risk. A cross-sectional study of 101 postmenopausal Caucasian women not taking hormone therapy observed that higher levels of adiposity in postmenopausal women were associated with:[75]

- ✓ Increased circulating estrogens (E1 and E2)
- ✓ Increased VLDL-cholesterol, VLDL- and HDL-triglycerides, hs-CRP, IL-6
- ✓ Increased insulin resistance
- ✓ Decreased levels of adiponectin, insulin sensitivity, and HDL-cholesterol
- ✓ Mean serum estradiol correlated significantly with adiposity
    - 3.26 pg/mL (12 pmol/L) Normal weight, 19 kg adipose tissue
    - 4.55 pg/mL (17 pmol/L) Overweight, 28 kg adipose tissue
    - 8 pg/mL (29 pmol/L) Obese, 39 kg adipose tissue

Cross-sectional studies confirm that observed serum lipid changes are associated with menopause and not just with aging. These changes include an increasingly atherogenic profile that includes more smaller, dense LDL particles, increased intermediate density lipoproteins, LDL, remnant and LDL cholesterol, and elevated glycA, a systemic inflammatory marker.[76]

Research suggests that the concentration of small dense LDL particles can increase by 30-49% in menopause. Despite a general decline in HDL, smaller denser HDL particles increase, compromising reverse cholesterol transport. [77]

The 2020 European Menopause and Andropause Society (EMAS) clinical guide for menopausal women with dyslipidemia notes that cardiovascular risk is greatest in those experiencing early menopause (before age 45). This risk is associated with adiposity, insulin resistance, hyperglycemia, and an atherogenic lipid profile characterized by increased triglycerides and total and LDL-cholesterol, and decreased HDL-cholesterol.[78]

A 5-6% reduction in LDL-C, along with a 3% increase in HDL-C can improve CVD outcomes according to a number of published meta-analyses.[79]

Women's Health Across the Nation Study

The Women's Health Across the Nation (SWAN) study of 2659 women noted alterations in serum lipids observed in the peri- and postmenopausal period.[80]

- ✓ Total and LDL cholesterol were lowest, and HDL-C was highest in the highest quartile of estradiol.
- ✓ Levels of total cholesterol, LDL cholesterol, triglycerides, and lipoprotein(a) peaked during the late perimenopausal and early postmenopausal period.
- ✓ Average cholesterol increased by 9.33 mg/dL (0.24 mmol/L) during the transition from pre- to late-perimenopause whereas normal aging of 4.84 years was only associated with an increase of 6.52 mg/dL (0.17 mmol/L).

- ✓ Researchers suggest lipid changes over time are attributable to the mean 33.5 pg/mL (123 mmol/L) reduction in estradiol and the mean 34.8 IU/L increase in FSH that occurs during the transition from premenopause to late perimenopause.

SWAN[81]	Pre-menopausal	Early peri-menopausal	Late peri-menopausal	Early post-menopausal	Late post-menopausal	Estradiol less than 21.45 pg/mL 78.74 pmol/L	Estradiol greater than 78.62 pg/mL 288.61 pmol/L
Total cholesterol mg/dL mmol/L	196.7 5.09	197.4 5.11	205.5 5.32	206.3 5.34	205.2 5.31	202 5.23	196.2 5.08
LDL-C mg/dL mmol/L	116.3 3.01	115.5 2.99	121.7 3.15	123.4 3.2	123.1 3.19	120.5 3.12	113.9 2.95
HDL-C mg/dL mmol/L	57.7 1.49	58.4 1.51	59.6 1.54	58.7 1.52	57.7 1.49	57.9 1.50	59.0 1.53
Lipoprotein (a) mg/dL	30.3 1.08	30.1 1.07	32.1 1.15	30.9 1.1	30.3 1.08	30.4 1.09	30.3 1.08
Triglycerides mg/dL mmol/L	100.2 1.13	103.3 1.17	105.8 1.2	106.4 1.2	106.4 1.2	104.3 1.18	102.0 1.15

A cross-sectional study of 444 postmenopausal women revealed a significant association between severity of symptoms and serum triglycerides, testosterone, and progesterone.[82]

- ✓ Elevated triglycerides were associated with severe symptoms
  - Past research also notes elevated triglycerides correlate with depression, decreased sexual desire, dry skin, and increased sweating.
- ✓ High levels of testosterone were associated with severe psychological symptoms and total MRS scores.
- ✓ Low progesterone was associated with severe symptoms.
- ✓ Decreased progesterone may be associated with increased urogenital, psychological, and total menopausal symptom scores.

Beyond Hormone Testing in Menopause

Biomarkers associated with chronic disease and inflammation should be incorporated into a comprehensive assessment of menopause. Early identification of risk factors provides the patient and practitioner the opportunity to address and modify risk early on.

Adipokines

Adipose tissue is now recognized as a metabolically active endocrine organ containing mature and premature adipocytes, endothelial cells, fibroblasts, and immune cells including mast cells. Adipokines are biologically active molecules that are produced primarily in adipose tissue but have systemic effects on inflammation, and lipid and glucose metabolism. Adipokine balance can become impaired as adipose tissue expands, and this imbalance contributes to a "metabolically unhealthy" obese state. A pro-inflammatory profile contributes to cardiovascular disease, metabolic syndrome, and type 2 diabetes.[83]

Main adipokines are:

- ✓ Adiponectin
- ✓ Chemokine ligand 2
- ✓ Interleukin-6. Interleukin-10
- ✓ Leptin
- ✓ Resistin
- ✓ Transforming growth factor-B
- ✓ Tumor-necrosis factor

Adipokines participate in regulation of blood pressure, blood clotting, immune function, inflammatory reactions, and lipoprotein metabolism. Notable changes in adipokine production occur in menopause. These changes are characterized by biochemical shifts that can be monitored:[84]

- ✓ Significant increases in leptin and resistin
- ✓ Downregulation of adiponectin and ghrelin
- ✓ Increased associated risk of dyslipidemia, hypertension, osteoporosis, and CVD

Leptin in Menopause

Leptin levels correlate with inflammation and are increased in chronic inflammatory disorders.[85]

Increased leptin correlates with increased abdominal obesity, visceral fat, and waist-to-hip ratio. Metabolic syndrome is associated with elevated leptin as well. In one study of 153 postmenopausal women, those with metabolic syndrome had significantly higher leptin. Levels correlated with increased visceral fat, abdominal obesity, and waist-to-hip ratio after adjustment for BMI.[86] Monitoring leptin levels during menopause may help assess cardiometabolic disease risk in postmenopausal women.

Adiponectin in Menopause

Researchers suggest that assessing adiponectin may be a good screening tool for metabolic syndrome during the menopausal period, especially when increased abdominal adiposity is present.

In a cross-sectional study of 290 peri- and postmenopausal women, adiponectin was significantly lower in those with metabolic syndrome at a mean level of 6.0 versus 9.2 ug/mL. Subjects in the lowest quartile of adiponectin (less than 4.5 ug/mL) also had significantly higher fasting glucose and triglycerides, and significantly lower HDL than those in the highest quartile (greater than 11.3 ug/mL). Researchers suggest that an adiponectin of less than 7.15 ug/mL is indicative of metabolic syndrome. Low levels of adiponectin can lead to:[87]

- ✓ Increased TNF-alpha and IL-6 from macrophages
- ✓ Chronic inflammation and insulin resistance
- ✓ Increased gluconeogenesis and hyperglycemia
- ✓ Decreased transport of free fatty acids within the cell
- ✓ Decreased anti-inflammatory IL-10 and IL-1-receptor antagonist
- ✓ Loss of adiponectin's anti-inflammatory effects on macrophages, cardiac muscle cells, fibroblasts, and the endothelium.

Anti-Mullerian Hormone in Menopause

Anti-Mullerian hormone (AMH) may provide insight into the timing of menopause, including premature ovarian failure. It is considered a very stable marker and levels will begin to decline earlier than FSH and inhibins. Levels of AMH may become barely detectable five to six years prior to full menopause.

Researchers found AMH decreased from above 1.5 ng/mL (10.7 pmol/L) to less than 0.2 ng/mL (1.4 pmol/L) approximately 5.99 years prior to menopause in women 45-48 years, and 9.94 years prior in women 35-39. Smoking will magnify decreases in AMH and can hasten menopause by up to three years.[88]

Bone markers in Menopause

Osteoporosis and related fractures are of significant concern in the postmenopausal period and outweigh the incidence of myocardial infarction, stroke, and breast cancer in this group combined.[89]

Bone mineral density can be assessed using bone density scans, though they may not reflect subtle changes in bone metabolism. Monitoring bone turnover markers in those at elevated risk for osteoporosis or those receiving therapy may be useful.

Since estrogen inhibits bone breakdown, its protective effects are diminished in menopause and increased bone breakdown by osteoclasts is observed. Elevations in bone matrix peptides such as C-terminal telopeptide (CTX) and procollagen type I N-terminal propeptide (P1NP), osteocalcin, bone-specific alkaline phosphatase should be further evaluated and addressed appropriately. Ideally a series of results should be compared to baseline in order to determine pathological trends, or response or resistance to treatment.[90]

The Association for Clinical Biochemistry & Laboratory Medicine summarizes changes in serum markers that represent increased risk of bone loss after menopause.[91]

Serum Biomarker	Premenopausal	Postmenopausal
CTX	0.19 ng/mL	0.31 ng/mL
P1NP	30.1 ng/mL	41.3 ng/mL
Bone alkaline phosphatase	9.8 ng/mL	14.1 ng/mL
Osteocalcin	17.9 ng/mL	24.5 ng/mL
25-OH vitamin D	31.5 ng/mL 78.6 nmol/L	26.5 ng/mL 66 nmol/L
PTH	27 pg/mL	34.9 pg/mL

Homocysteine in Menopause

Postmenopausal status (55 years or older) is associated with elevated homocysteine, a biomarker associated with increased risk of hypertension and CVD. Elevated homocysteine itself is associated with decreased HDL, vitamin C, red blood cell folate, and serum folate and B12. Intake of vitamin and mineral supplements is associated with a decrease in homocysteine levels.[92]

Alterations in homocysteine metabolism observed across stages of menopausal transition can contribute to endothelial dysfunction and its cardiovascular complications. In one study of healthy women categorized as pre-, peri-, and postmenopausal, declining estradiol was associated with an elevation in homocysteine and cysteine. Both biomarkers are associated with endothelial dysfunction. In this study, homocysteine and cysteine were inversely correlated with estradiol, glutathione, brachial artery flow-mediated dilation, and intake of vitamins B6 and B12. Elevations in homocysteine and cysteine were correlated with elevations in oxidized LDL as well, increasing risk of atherosclerosis and CVD.[93]

Oxidative Stress in Menopause

Oxidative stress is a recognized risk factor for chronic disease including atherosclerosis, CVD, vasomotor disorders, and neurological disease. Menopause has been associated with an increase in oxidative stress, possibly due to loss of the antioxidant effects of estrogen. A case-controlled study of 50 postmenopausal and 48 premenopausal women demonstrated a significantly lower serum total antioxidant capacity, and significantly higher level of the oxidative stress marker malondialdehyde, in the postmenopausal group.[94]

Increases in glycation end-products (AGEs) and other oxidative stress biomarkers are observed with menopause and associated with increased risk of subclinical atherosclerosis:[95]

- ✓ Significantly higher AGEs were observed in women with higher testosterone of 53-60 ng/dL (1.7-5.6 nmol/L) versus lower testosterone of 23-52 ng/dL (0.8-1.8 nmol/L).
    - Increased free androgen index (FAI), was also associated with increased AGEs. The correlation remained highly significant even after adjustment for HOMA-IR, fasting glucose and insulin, age, and BMI.[96]
- ✓ Asymmetric dimethylarginine (ADMA), which inhibits nitric oxide synthase, increased with BMI in postmenopausal women.
- ✓ Ischemia modified albumin (modified by oxygen free radicals) was elevated in obese postmenopausal women.
- ✓ Oxidative stress itself contributes to CVD, diabetes, hypercholesterolemia, and hypertension.

Monitoring gamma-glutamyltransferase (GGT) can help assess risk of oxidative stress and metabolic dysfunction as well. Increased serum GGT is associated with increased glutathione metabolism, decreased glutathione levels, and increased oxidative stress.[97] Levels above 16.5 U/L are associated with metabolic syndrome and above 20.5 U/L are associated with impaired glucose tolerance.[98]

Oxidative stress appears to contribute to postmenopausal osteoporosis (PO). A systemic review and meta-analysis revealed that those with PO had: [99]

- ✓ Significantly elevated oxidative stress index, malondialdehyde, advanced oxidation protein products, and vitamin B12.
- ✓ Decreased total antioxidant status, total antioxidant power, catalase, glutathione peroxidase, uric acid, and folate.

Sex Hormone Binding Globulin in Menopause

A prospective longitudinal cohort study of 172 women found that while testosterone did not change from the pre- to postmenopausal period, SHBG decreased by 43% from 4 years prior to their final menstrual period to two years after. This shift increased the free androgen index by 80% during this period. The decreased SHBG and increased FAI correlated with an increase in BMI. Lower levels of DHEAS were also associated with a higher BMI.[100]

Decreased SHBG and higher BMI are associated with increased risk of metabolic syndrome in postmenopausal women. Evaluation of data from the Women's Health Study revealed that 51% of postmenopausal women, not on hormone therapy, met the criteria for metabolic syndrome. This group had significantly lower SHBG, higher BMI, more cardiovascular events, and significantly higher estradiol, testosterone, and free androgen index:[101]

TSH in Menopause

Some symptoms of menopause overlap with those of thyroid dysfunction which should be ruled out. Thyroid stimulating hormone (TSH) levels are positively associated with dyslipidemia in postmenopausal women e.g., elevated triglycerides, LDL, and total cholesterol. Because iodine uptake into the thyroid gland decreases during menopause, production of thyroid hormone decreases and in response, TSH increases. Thyroid hormones exert specific effects including:[102]

- ✓ Increases synthesis of androgens, thyroid-binding globulin, and SHBG
- ✓ Reduces sex steroid clearance
- ✓ Stimulates aromatase

Vitamin D in Menopause

Vitamin D insufficiency is common in menopause and is associated with autoimmunity, cancer, diabetes, hypertension hypertriglyceridemia, immune compromise, impaired calcium metabolism, inflammation, metabolic syndrome, multiple sclerosis, osteoporosis risk, psoriasis, and rheumatoid arthritis.[103] Low serum 25(OH) vitamin D is also associated with depression and impaired cognition, also commonly observed with menopause.[104]

Low levels of 25(OH)D are also correlated with increased bone turnover in postmenopausal women. In one double-blind placebo-controlled study, supplementation with 1000 IU/day of vitamin D resulted in increased serum 25(OH)D from 15 ng/mL (37.4 nmol/L) to 27.5 ng/mL (68.6 nmol/L), along with decreases in serum PTH, CTX, and P1NP.[105] It is noted that levels did not reach the minimum recommended functional level of 40 ng/mL (100 nmol/L).[106]

Ensuring optimal vitamin D status with levels maintained between 50-90 ng/mL (125-225 nmol/L) can help minimize the risk of many chronic conditions associated with menopause. Therefore, vitamin D status should be monitored regularly in menopause and beyond.

Natural Approaches to Menopause

Though hormone replace therapy tends to be the "go to" in allopathic medicine, it's possible to resolve some discomfort through more natural means as a first step. It's equally important to address a menopausal woman's increased risk of chronic disease by encouraging nutrition and lifestyle patterns that optimize health as well as assist in symptom management.

A 2016 EMAS position statement proposes a holistic framework for the management of a healthy menopause (HM). Healthy diet and lifestyle, physical activity, stress management, and education are the cornerstones of the HM approach. The HM model incorporates a multidisciplinary team that ultimately addresses social and psychological function, as well as physical function and morbidity. A variety of healthcare disciplines should be represented including naturopathic, osteopathic, chiropractic, as well as physiotherapy, homeopathy, and traditional Chinese medicine.[107] Prevention of chronic disease is a significant focus of this holistic approach.

Clearly, menopause can't be prevented but its negative effects can be managed, and chronic disease risk can be reduced. Basic evidence-based approaches to disease prevention include: [108]

- ✓ Alcohol intake moderation
- ✓ Exercise
- ✓ Healthy diet
- ✓ Mental stimulation
- ✓ Smoking cessation
- ✓ Social engagement

More than half of menopausal women seek complementary and alternative approaches to managing menopause and perceived effectiveness is greater than 60%. Approaches include[109]

Mind-body	Natural products	Whole system approaches
✓ Biofeedback ✓ Cognitive behavioral therapy (CBT) ✓ Essential oils, aromatherapy ✓ Hypnosis ✓ Meditation ✓ Mindfulness-based stress reduction ✓ Relaxation ✓ Yoga	✓ Dietary supplements ✓ Herbs ✓ Vitamins, minerals	✓ Acupuncture ✓ Homeopathy ✓ Reflexology ✓ Traditional Chinese medicine

Overview of Natural Approaches to Menopause[110]

- ✓ Hypnosis fared well in randomized controlled trials (RCTs) for reducing hot flashes and improving sleep and sexual function and has been recommended by the North American Menopause Society.[111]
- ✓ Cognitive behavioral therapy was effective for reducing the disruptive aspects of hot flashes but not their frequency.
- ✓ Relaxation techniques may benefit stress management and vasomotor symptoms, but available research was limited.
- ✓ Mindfulness-based stress reduction yielded clinically meaningful improvement in sleep quality, anxiety, perceived stress, and overall quality of life.
- ✓ RCTs revealed that practicing yoga significantly reduced symptoms on the Menopause Rating Scale and improved fatigue and overall quality of life.
- ✓ Reflexology significantly improved vasomotor and sexual dysfunction symptoms and reduced hot flash frequency by 56% in a 12-week RCT of 120 menopausal women.
- ✓ Acupuncture was found to improve somatic, sleep, and vasomotor symptoms in six RCTs of menopausal women.

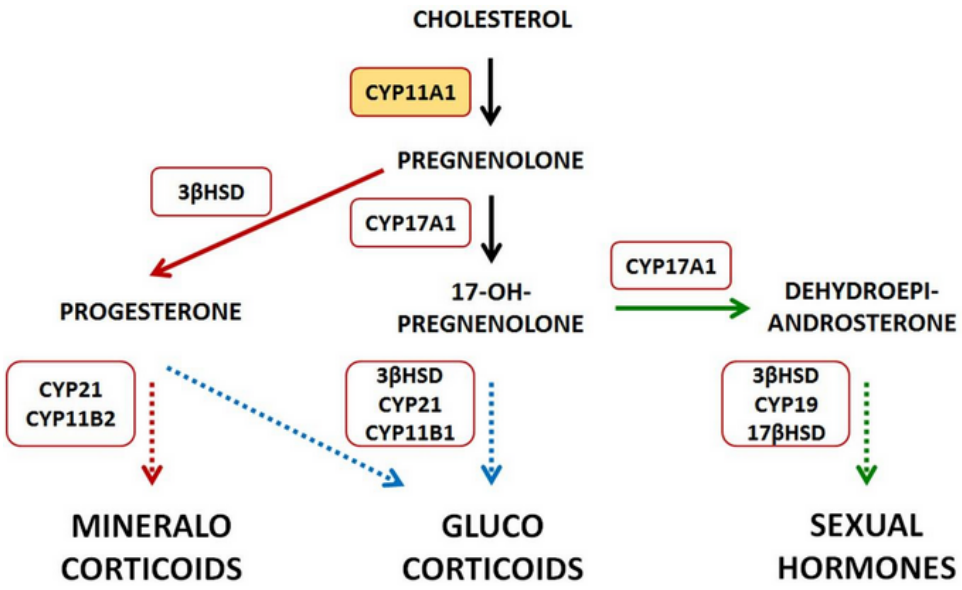
- ✓ Lavender essential oil reduced hot flashes by 50% compared to 1% in the placebo group in a double-blind crossover trial of 100 women.
    - Research also demonstrated improvements in sleep, physical, and psychological symptoms using lavender oil.
- ✓ Efficacy and benefits of massage were enhanced with the use of aromatherapy as noted in randomized trials.
- ✓ Herbal therapies
    - Black cohosh (Cimicifuga racemose) has been studied for its effects on menopausal symptoms though systematic review of randomized controlled trials found insufficient conclusive evidence for using black cohosh alone. However, one trial that combined black cohosh with St. John's wort revealed 50% improvement in Menopause Rating Scale scores and significant reductions in depression.
    - Wild yam (Dioscorea) has been used in traditional Chinese Medicine for addressing menopausal symptoms, though the amount of clinical research available is limited.
        - One randomized controlled study reported 90% improvement in menopausal symptoms (primarily psychological) with the use of 12 grams of Dioscorea alata taken twice daily.
    - Dong Quai (Angelica sinensis) has been used in traditional Chinese medicine to address female reproductive issues.
        - A randomized controlled study of Dong Quai combined with Matricaria chamomilla demonstrated 90-96% improvement in hot flash frequency and intensity. Dong Quai combined with American ginseng, black cohosh, chasteberry milk thistle, and red clover was associated with a 73% reduction in hot flashes and a 69% reduction in night sweats in a 12-week double-blind placebo-controlled randomized trial of 50 women who also reported improved sleep quality.
    - Phytoestrogens found in soy, red clover, hops, flaxseed had mixed results in heterogenous studies. Researchers recommend an expansion of more standardized research to full assess their application in menopause therapy.
    - Traditional Chinese medicine herbs had mixed results with some studies reporting improvement in vasomotor symptoms, sexual functioning, tension, insomnia, and depression.
    - Additional CAM therapies that warrant further study include Maca (of the brassica family), pollen extract, vitamin E, and homeopathy.
    - Review of side effects and contraindications should be integrated into herbal therapy care plans.

Additional Research on Natural Approaches to Menopause:[112]

- ✓ Cognitive behavioral therapy was found to decrease the perceived impact of vasomotor symptoms by 50% with 8 hours of therapy over a 4-6 week period. Positive effects were sustained through at least six months. Although both self-help and group approaches were efficacious in reducing vasomotor symptoms, the in-person group setting was more beneficial in terms of quality of life improvements. The NAMS recommends CBT for vasomotor symptoms.
- ✓ Hypnotherapy was associated with a statistically significant decrease in vasomotor symptoms (subjective and objective) following 5 weekly one-hour sessions and some additional "homework.". An overall 80% reduction in hot flush frequency was reported versus just 15% reduction in controls.
- ✓ Mindfulness and relaxation had limited research, however a randomized controlled study of 110 women did not find significant improvement in vasomotor symptoms following 20 hours of mindfulness-based stress reduction.
- ✓ A double-blind, randomized controlled trial with 63 women found that the combination of red clover isoflavone and probiotic statistically reduced hot flushes by 4.3 occurrences per day.
- ✓ An older review did not find black cohosh efficacious for reducing hot flushes, though a 2020 study used it successfully in combination with 3 other herbs. Women with breast cancer are advised to avoid isoflavones and black cohosh by the NICE guidelines.
- ✓ Exercise was not found to specifically improve vasomotor symptoms associated with menopause. However, exercise and yoga were found to improve sleep quality and exercise improved mood.
- ✓ Acupuncture was associated with an improvement in vasomotor symptoms that was greater than no treatment at all. However, a randomized trial of 10 consecutive treatments found only a non-statistical benefit of acupuncture versus sham treatment.

DHEA

Dehydroepiandrosterone sulfate, the sulfated form of DHEA, is the most abundant steroid in circulation with levels peaking between 20 and 30 years of age at a level of approximately 370 ug/dL (10 umol/L).[113] It is an important precursor to testosterone and estrogen, including in the postmenopausal period.[114] DHEA supplementation may have a positive effect on body composition, cognitive performance, sexual function, and cardiovascular symptoms though these benefits may vary due to ethnicity.[115]



Schematic overview of the steroid hormone biosynthesis

Neunzig, Jens, and Rita Bernhardt. "Dehydroepiandrosterone sulfate (DHEAS) stimulates the first step in the biosynthesis of steroid hormones." PloS one vol. 9,2 e89727. 21 Feb. 2014, doi:10.1371/journal.pone.0089727 [R] This is an open-access article distributed under the terms of the Creative Commons Attribution License.

DHEAS is the most frequently studied adrenal androgen in perimenopausal studies. Though circulating DHEAS decreases by approximately 80% from age 20 to age 70, it begins to rebound in women transitioning through menopause though levels can decrease again postmenopause. Evaluation of the SWAN study data noted ethnic differences in circulating DHEAS with the highest levels occurring in Chinese subjects, and lowest levels in African American and Hispanic subjects. Higher BMI was associated with lower DHEAS in general. Changes in DHEAS levels correlated with shifts in circulating testosterone and estrogen.[116]

Higher levels of DHEAS were associated with enhanced physical function and quality of life, and fewer symptoms of depression.[117]

According to the position paper of the Polish Menopause and Andropause Society, DHEA supplementation is effective or likely effective in postmenopausal women with:[118]

- ✓ Adrenal insufficiency
- ✓ Depression and anxiety
- ✓ Hypoactive sexual disorder
- ✓ Low bone mineral density and/or osteoporosis
- ✓ Obesity, insulin resistance
- ✓ Vulvovaginal atrophy
- ✓ 25-100 mg/day in split doses can be effective, but supplementation is contraindicated in
    - Breast cancer or history of breast cancer
    - Vaginal bleeding, untreated endometrial hyperplasia

Diet and Nutrition

Nutrient insufficiency is a chronic issue globally and is highlighted in the Dietary Guidelines for Americans despite the perceived affluence of the United States. Commonly under-consumed nutrients in women of child-bearing age include calcium, choline, dietary fiber, magnesium, potassium, iron, and vitamins A, C, D, and E. Wisdom does not always come with age. Perimenopausal and menopausal women also have intakes that fall significantly short of estimated average requirements (EARs), including calcium, magnesium, and vitamins A, D, and E. Those with the lowest intake of folate, vitamin D, B12, and DHA had the lowest blood levels of these nutrients as well. [119]

Serum levels of nutrients and their metabolites provide valuable insight into nutrient bioavailability and nutrition status and should be incorporated into a comprehensive health assessment for pre- and postmenopausal women. Dietary supplementation can and should fill in the gaps for consistently insufficient intake or impaired absorption. Supplementation is also associated with better health and lifestyle choices.

An in depth review of 19 studies revealed that a greater intake of unprocessed foods, vegetables, and whole grains was associated with less severe vasomotor, somatic, urogenital, and psychological symptoms. Sleep quality was also improved. On the other hand, increased severity of symptoms was associated with increased intake of processed foods, sugar, and saturated fats. These results are consistent with the concept that a healthy diet contributes to healthy physiology and metabolism.[120]

Prudent guidelines for menopausal women include:[121]

- ✓ Antioxidants from plant-based foods
  - Almonds, artichokes, blackberries, blueberries, sour cherries, chokeberry, dark chocolate, cloves, cranberries, coffee, grape juice, pomegranate juice, pecans, raspberries, spinach, strawberries, walnuts, spices, red wine (moderation)
- ✓ Omega-6s from seeds, nuts
- ✓ Omega-3s from nuts, flax, fish, seafood
  - Herring, mackerel, sardines, salmon, trout, toothfish
- ✓ Phytonutrients
  - Allicin found in garlic, chives, leeks, onions
  - Capsaicin found in hot peppers
  - Carotenoids including beta-carotene, lycopene, lutein
  - Curcumin found in turmeric
  - Flavonoids found in berries, black and green tea, celery, citrus fruit, olives, onions, oregano, purple grape juice, soybeans, vegetables, whole wheat, wine (in moderation)
- ✓ Genistein and daidzein isoflavones found in soybeans, soy flour, soymilk, tofu, textured vegetable protein, legumes
- ✓ Indole organosulfur compounds found in cruciferous vegetables including broccoli, Brussels sprouts, cabbage, cauliflower, horseradish, mustard greens, kale
- ✓ Isothiocyanate organosulfur compounds from cruciferous vegetables
- ✓ Monoterpenes from citrus peels and oils
- ✓ Phenolic acids from coffee beans, apples, blueberries, cherries, grapes, oranges, pears, prunes, oats, potatoes, soybeans
- ✓ Resveratrol found in red wine, peanuts, grapes, raspberries
- ✓ Saponins found in soybeans, alfalfa and other sprouts, green vegetables, potatoes, tomatoes
- ✓ Tannins found in black-eyed peas, grapes, lentils, wine, tea
- ✓ Probiotics
- ✓ Protein intake of 1-1.2 g/kg

Mediterranean diet

The Mediterranean diet is a good example of a healthy foundation for optimal nutrition. The European Menopause and Andropause Society position statement strongly supports the Mediterranean diet for menopausal health and management and provides the following position paper:[122]

> The Mediterranean diet is a non-restrictive dietary pattern common in the olive-growing areas of the Mediterranean basin. It may improve vasomotor symptoms, cardiovascular risk factors such as blood pressure, cholesterol and blood glucose levels, as well as mood and symptoms of depression. Long-term adherence may: improve cardiovascular risk and events, and death; improve bone mineral density; prevent cognitive decline; and reduce the risk of breast cancer and all-cause mortality

An updated, more environmentally-friendly Mediterranean Diet Pyramid addresses human and environmental health. The update strongly emphasizes decreased consumption of red meat and bovine dairy productions, and increased consumption of legumes and sustainably grown plant-based foods.[123]

Serra-Majem, Lluís et al. "Updating the Mediterranean Diet Pyramid towards Sustainability: Focus on Environmental Concerns." International journal of environmental research and public health vol. 17,23 8758. 25 Nov. 2020, doi:10.3390/ijerph17238758 [R] This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license ([R]).

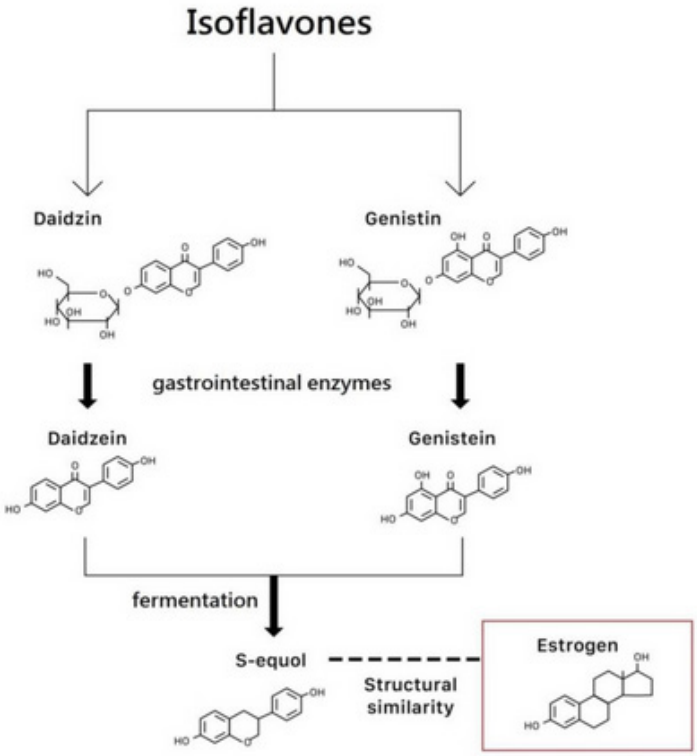
Supplementation[124]

- ✓ Vitamin D supplementation in deficient menopausal women reduced hyperglycemia, hypertriglyceridemia, and overall metabolic syndrome profile.
- ✓ Vitamin E supplementation of 800 IU per day may reduce hot flushes, improve sleep quality, and relieve vaginal atrophy.
- ✓ Micronutrient supplementation with B vitamins, vitamin C, magnesium, zinc, and essential fatty acids may reduce stress and anxiety in menopause.
- ✓ Polyphenols from hops or grapeseed, and mussel extracts may relieve vasomotor and other menopausal symptoms.

Phytoestrogens

Phytoestrogens are compounds found in plants that can have an estrogen-like effects in the body. Isoflavones act as phytoestrogens and can be found in soybeans (genistein and daidzein), red clover, and alfalfa. Lignans found in fruits, vegetables, whole grains, and flax seeds, also act as phytoestrogens. Because of the nature of their receptor-based mechanisms, phytoestrogens exert estrogenic and antiestrogenic effects and ultimately are considered safe and possibly protective against hormone-related cancers.[125]

Isoflavones have shown promise in reducing vasomotor symptoms, moderating lumbar spine loss, and improving bone mineral density.[126] Though not as clinically effective as hormone replacement therapy, phytoestrogens may be an option for women seeking a non-hormonal approach to menopause.



Chen, Li-Ru, and Kuo-Hu Chen. "Utilization of Isoflavones in Soybeans for Women with Menopausal Syndrome: An Overview." International journal of molecular sciences vol. 22,6 3212. 22 Mar. 2021, doi:10.3390/ijms22063212 [R] This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license ([R]).

Isoflavones can bind to estrogen receptors with a weak affinity for ER-alpha (predominantly found in the breast and uterus), and a stronger affinity for ER-beta (predominantly found in bone, urogenital tract, and the cardiovascular system). Systematic review reveals that though the mechanism of action for isoflavones in menopause is not completely understood, supplementation is beneficial for many individuals. The NAMS recommends a trial of isoflavones of at least 50 mg per day for 12 weeks with a continuation of therapy if benefits are significant.[127]

One study of 20 postmenopausal women found that daily intake of 69 milligrams of soy isoflavones increased low normal levels of SHBG from 55.5 nmol/L to 64.2 nmol/L in women maintaining a serum isoflavone level of at least 0.6 umol/L.[128]

Systematic review and meta-analysis comprising 2305 postmenopausal women in 29 studies evaluated the effect of soy isoflavone extract and isoflavone-rich soy protein isolate on serum lipids. Analysis demonstrated a significant reduction in total cholesterol and significant increase in HDL-C. Reductions in LDL-C and triglycerides were also observed.[129]

A double-blind, placebo-controlled trial of 78 symptomatic menopausal women evaluated the effects of 190 mg of a combined soy and hop isoflavone extract on menopausal symptoms. Results revealed a 20.6 point improvement in symptoms score with treatment compared to 14.8 points in the placebo group. These women experienced significant improvement in pain, palpitations, fatigue, paresthesia, and vaginal dryness.[130]

Herbal Medicine

Herbal medicine has been used by humans for thousands of years without knowing the full mechanism of action, though that does not negate their effectiveness. The following uses have been identified for menopausal symptoms: [131]

✓	Actaea racemose	Hot flashes, insomnia, irritability, musculoskeletal pain
✓	Gingko biloba:	Attention deficits
✓	Panax ginseng:	Depression, sexual function, sleep disorders
✓	Valerian officinal	Anxiety, dysmenorrhea, hot flashes, sleep disorder

Mounting research reveals herbal formulas can effectively address menopausal symptoms as well as improve metabolic profiles.

A 2017 literature review of clinical trials revealed that several medicinal plants were effective in addressing acute menopausal symptoms including:[132]

- ✓ Alfalfa
- ✓ Black cohosh
- ✓ Black cumin
- ✓ Evening primrose
- ✓ Fennel
- ✓ Fenugreek
- ✓ Ginkgo biloba
- ✓ Glycine soja
- ✓ Hypericum perforatum (St. John's wort)
- ✓ Lemon balm
- ✓ Licorice
- ✓ Panax ginseng
- ✓ Passiflora incarnata
- ✓ Pimpinella anisum
- ✓ Red clover
- ✓ Sage
- ✓ Valerian
- ✓ Vitex

In one randomized, double-blind, placebo-controlled trial of 111 postmenopausal women, 12 weeks of supplementation with black cohosh, chasteberry, evening primrose oil, and soy isoflavones significantly reduced hot flashes, sweating, sleep issues, irritability, and depressed mood. Although hormone levels remained similar between subjects and controls, levels of CRP, LDL-cholesterol, and triglycerides were significantly reduced in the active group.[133]

Meta-analysis and review of 19 randomized controlled studies revealed that Chinese herbal medicine reduced menopausal symptoms effectively even though no statistically significant differences in hormone levels occurred. The analysis concluded that herbal intervention significantly improved vasomotor symptoms, quality of life, and upper-body peripheral blood flow.[134]

Characteristic of Herbal Derivatives used to Alleviate Menopause Symptoms

Herbal Derivatives			
Scientific Name	**Common Name**	**Effects**	**Side Effects**
Actaea racemosa	Black cohosh	Treatment of menopause symptoms such as hot flash, insomnia, irritability, but also musculoskeletal pain, fever, cough.	Gastrointestinal discomfort.
Evening Primrose Oil	Oenothera biennis oil	Treatment for menopausal and premenstrual symptoms, but also for atopic dermatitis and rheumatoid arthritis.	Gastrointestinal disorders and interaction with antiepilectic drugs.
Foeniculum vulgare	Fennel	Treatment of hot flashes, anxiety, and vaginal atrophy.	No side effects reported.
Ginkgo biloba	Ginkgo	Treatment of attention disorders in postmenopausal women.	Gastrointestinal disorders, allergic reactions, headache, and lowering of seizure threshold.
Glycyrrhiza glabra	Licorice	Treatment of hot flash duration.	Cardiovascular disease, hypercortisolism, hypokalemia, and hypernatremia.
Hypericum perforatum	St. John's Wort	Treatment for the vasomotor symptoms of postmenopausal women.	Gastrointestinal disease, sensitivity to light, fatigue.
Medicago sativa	Alfalfa	Effect on neurovegetative menopausal symptoms.	Possible infection with Salmonella, Escherichia coli, and Listeria.
Melissa officinalis	Lemon balm, bee balm or honey balm	Effect on anxiety.	No side effect reported.
Panax ginseng	Ginseng	Treatment of sleep disorders, depression, and sexual function.	Possible effect on endometrial thickness.
Passiflora incarnata	Passion fruit	Treatment of vasomotor symptoms, insomnia, anxiety and dysmenorrhea.	No side effect reported.
Pimpinella anisum	Anise	Treatment of hot flashes but it also exerts an antiulcer action.	No side effects reported.
Salvia officinalis	Sage herb	Treatment of hot flashes and sweats.	Possible interaction with diabetes and blood pressure.
Trifolium pretense	Red clover	Treatment of hot flashes and it also exerts a bone preventing loss.	No side effects reported.
Trigonella foenum	Fenugreek	Treatment for hot flashes and osteopenia.	No particular side effects.
Valerian officinalis	Valerian	Useful for hot flashes, anxiety, sleep disorders and dysmenorrhea.	No side effects reported.
Vitex agnus-castus	Chaste tree, chasteberry or monk's pepper	Treatment for vasomotor symptoms and sleep diseases.	Not reported.

De Franciscis, Pasquale et al. "A Nutraceutical Approach to Menopausal Complaints." Medicina (Kaunas, Lithuania) vol. 55,9 544. 28 Aug. 2019, doi:10.3390/medicina55090544 [R] This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license ([R]).

Lifestyle

Optimization of nutrition status, weight maintenance, stress management, physical activity, and sleep reduces the risk or severity of many of the conditions associated with menopause.

Healthy dietary changes and increased physical activity represent the "therapeutic ideal" for improving insulin sensitivity, reducing central adiposity, and optimizing adipokines in the menopausal period.[135] Though breaking old habits and adopting new ones can be a challenge, the results are well worth the effort and may effectively reduce the morbidity associated with postmenopause.

Maintaining a healthy weight through healthy changes could literally be lifesaving. Obesity and excess body fat are associated with chronic low level inflammation which, in turn, is associated with cancer and cardiometabolic disease. Lifestyle changes that promote weight loss were found to reduce inflammatory markers in overweight postmenopausal women.

The SHAPE-2 Trial demonstrated a significant decrease in hs-CRP from 1.99 mg/L to 1.75 mg/L in overweight postmenopausal women who lost weight on a hypocaloric diet. Levels of hs-CRP decreased significantly from 1.85 mg/L to 1.37 mg/L in the women who lost weight mainly through exercise. Levels of leptin also decreased significantly with diet and exercise.[136]

Sleep

Sleep disorders associated with menopause can be part of a perpetual cycle. Decreased levels of estrogen can lead to vasomotor symptoms, depression, and anxiety that interrupt sleep. The loss of sleep can then contribute to anxiety, depression, and increased risk of obesity, impaired glucose tolerance, type 2 diabetes, hypertension, and CVD. Researchers identified targeted nutrition therapies that may improve sleep and reduce disease risk in postmenopausal women.

Maintenance of a healthy weight, glucose regulation, omega-3 intake, and adequate intake of tryptophan which is converted to serotonin and then melatonin is fundamental to a healthy menopausal transition. Intake of food-based tryptophan improved sleep in elderly volunteers with disordered sleep. Researchers recommend 3.5-6 mg of tryptophan per kg of body weight.[137]

Tryptophan per 100g of food

Milk 42 mg
Wheat flour 110 mg
Eggs 165 mg
Sausage 93 mg
Potato 28 mg
Cheese 325 mg
Beef 230 mg
Banana 10 mg
Soybeans 160 mg
Bread, oat bran 140 mg
Chia seeds 440 mg
Chicken, breast, skinless, boneless 400 mg
Cocoa 290 mg

Essential Oil Therapy

Essential oils contain volatile compounds that can positively affect human physiology, including a potential effect on neurotransmitter release.

The aromatic use of lavender was found to reduce symptoms in a randomized controlled trial of menopausal women. The subjects inhaled lavender two times per week for 20 minutes. Lavender is known to have anti-anxiety, sedative, and sleep-enhancing properties. In the study, inhalation of lavender significantly improved anxiety, depression, sexual desire, and physical and vasomotor symptoms.[138]

One systematic review found that lavender as aromatherapy or in capsule form can significantly improve sleep, sexual function, physical symptoms, depression, and anxiety in postmenopausal women. The majority of subjects reported feeling relaxed and happy after lavender use.[139]

The National Institute on Aging Addresses Hot Flashes:[140]

Sometimes hot flashes are tolerable if symptoms are mild. However, if symptoms seem intolerable, a 3-month trial of lifestyle changes is recommended before hormone therapy is considered.

General

- ✓ Dress in layers that can be removed.
- ✓ Carry a portable fan
- ✓ Avoid alcohol, caffeine, and spicy foods that may make hot flashes worse.
- ✓ Quit smoking
- ✓ Maintain a healthy weight
- ✓ Get adequate sleep, keep the room cooler at night, try a bed fan

Mind-body practices

- ✓ Yoga or tai chi have been found to improve menopausal symptoms
- ✓ Deep breathing, relaxation breathing
  - In a comfortable position, place one hand on the belly, one on the chest
  - Slowly inhale through the nose allowing the chest and belly to rise
  - Slowly exhale through the mouth, pressing gently on the chest and belly to exhale completely
  - Repeat for several minutes throughout the day and before falling sleep

Non-hormone options

- ✓ Selective serotonin reuptake inhibitors (SSRIs), low dose
  - Side effects may include dizziness, drowsiness, headache, jitteriness, nausea
- ✓ Benefits and risks of natural treatments such as black cohosh, DHEA, and phytoestrogens are still being studied.

Hormone therapy (lowest dose, shortest duration possible)

- ✓ Estrogen and progesterone replacement therapy may help treat hot flashes
- ✓ Increases risk of blood clots, breast cancer, dementia, gallbladder disease, heart attack, stroke, especially for postmenopausal women over age 60.
- ✓ Contraindications include
  - Breast or uterine cancer
  - History of blood clots, bleeding disorder, heart disease, heart attack, liver disease, stroke, vaginal bleeding, or current possibility of pregnancy.
- ✓ Forms include creams, gels, implants, patches, pills, rings.
  - Dermal patches may be safest for those at cardiac risk.
- ✓ Composition includes conjugated estrogen, estradiol, selective estrogen receptor modulators (SERMs), synthetic or compounded hormones.
- ✓ Side effects include bloating, breast tenderness, cramping, spotting or monthly periods.

Hormone Replacement Therapy (HRT)

Hormone replacement therapy (HRT), also known as menopausal hormone therapy (MHT), has been used as a primary approach to managing the vasomotor symptoms of menopause, especially within 10 years of menopause or for those under the age of 60:[141]

- ✓ Systemic estrogen is most effective for vasomotor symptoms
- ✓ Estrogen alone may be used following hysterectomy
- ✓ Unopposed estrogen may increase risk of endometrial hyperplasia and cancer in those with an intact uterus
- ✓ Concurrent progesterone is provided to reduce risk of uterine complications
- ✓ Transdermal versus oral delivery may be reduce risk of venous thromboembolism

For those women under age 60 or within 10 years of menopause, the risk to benefit ratio is more favorable than those older than 60. Potential negative consequences from HRT include thrombosis, stroke, and cancer of the breast.[142] Ideally HRT is reserved for those with moderate to severe menopausal symptoms.[143]

The majority of postmenopausal women will have a serum estradiol level of 9.3 pg/mL (34 pmol/L) or less without hormone replacement therapy.[144] Hormone therapy may be initiated if no contraindications are present.[145] Low dose oral contraception with an intact uterus may also be effective. The transdermal form of estradiol may be preferred if CVD risk factors are present, including hypertension, obesity, smoking, or risk of venous thromboembolism. Progestin/progestogen therapy for 10-15 days per 28 days is recommended if the uterus is intact.[146]

Estrogen therapy reduces total and LDL-cholesterol and increases HDL-cholesterol. However, the oral form can increase triglycerides, leading to an EMAS recommendation to provide transdermal estrogen to women with hypertriglyceridemia.[147]

Research suggests that HRT can modulate the proinflammatory profile associated with menopause.[148] This pattern is characterized by elevations in TNF-alpha, IL-6, and CRP.[149]

Dosing

Research indicates that hormone replacement therapy may be best administered at a low dose with an adjustment in dosing dependent on clinical response. A clinical goal for estradiol of 60 pg/mL (220 pmol/L) would be required to reduce risk of osteoporosis and reduce hot flashes by 50%. Serum levels depend on dosing and form of therapy. The following serum levels were achieved using oral estrogen therapy:[150]

Dose	Oral Estrogen Form	Serum Estradiol
1 mg	Estradiol	30-65 pg/mL 110-239 pmol/L
2 mg	Estradiol	60-110 pg/mL 220-404 pmol/L
0.45 mg	Conjugated estrogen	60 pg/mL 220 pmol/L
0.625 mg Considered standard dose, Equivalent to 1-2 mg oral estradiol	Conjugated estrogen	76.8 pg/mL 282 pmol/L

Women's Health Initiative clinical trials provided postmenopausal estrogen therapy in the form of conjugated equine estrogens (Premarin from pregnant mare urine) or conjugated equine estrogens plus synthetic medroxyprogesterone acetate (PremPro). A one year analysis of a subset of 200 subjects found: [151]

- Estrone levels increased by 4-fold in both therapy groups
- Estradiol increased by 3-fold in both therapy groups
- Bioavailable and free estradiol increased by 2-fold in both therapy groups
- SHBG increased by 2.5-fold in both therapy groups
- Progesterone decreased in the PremPro group (which was counterintuitive but possible due to decreased endogenous production)
- Researchers note variations in response to hormone therapy based on race, age, BMI, smoking status, baseline hormones, and reported vasomotor symptoms.

Researchers hope to target postmenopausal symptoms while minimizing systemic exposure to estradiol. Another option being researched is vaginal capsules of estradiol.[152]

Hormone therapy may reduce risk of future heart disease but should be combined with preventative measures for optimal effect. Management of menopause and perimenopause should focus on prevention of secondary complications and should include[153]

- ✓ Evaluation and monitoring of heart disease risk
- ✓ Blood pressure monitoring
- ✓ Fasting lipid profile
- ✓ Vitamin D status evaluation
- ✓ Optimization of lifestyle habits including diet and activity

North American and European Guidelines for Hormonal Management of Menopause

Key points from the 2017 North American Menopause Society (NAMS) Hormone Therapy Position Statement include:[154]	The European Menopause and Andropause Society (EMAS) position statement on management of menopause includes:[155]
Hormone therapy was most effective for vasomotor symptoms, genitourinary syndrome, prevention of bone loss, and reduction of bone fracture.	Estrogen is given alone if post-hysterectomy.
Ideal benefit to risk ratio for use of hormone therapy is in symptomatic women with no contraindications, who are under 60 or within 10 years of menopause.	Use of transdermal estrogen reduces risk of thromboembolism.
Benefit to risk ratio was less favorable for women 60 or older, or more than 10 years out from menopause due to increased risk of coronary artery disease, dementia, stroke, and venous thromboembolism.	Progestogens are added to reduce the risk of endometrial cancer in women who have not had a hysterectomy.
Dose, duration, route, and initiation of hormone therapy will determine absolute risk from treatment.	Use of progesterone or dydrogesterone instead of synthetic progestogens may reduce risk of venous thrombosis and breast cancer.
Therapy with estrogen alone may be more favorable than estrogen-progesterone therapy for prolonged treatment according to data from the Women's Health Initiative trials.	Synthetic steroids, antidepressants, hypotensives, anti-depressants, and selective estrogen modulators may be used as well.
Bioidentical, compounded hormone therapy may be minimally regulated.	Androgen therapy is controversial as MHT.
	HRT should be reviewed within 3 months and then annually.
	Average weight gain of 22 pounds (10 kg) from 40-60 years of age can be countered with regular exercise and a healthy diet abundant in fruits and vegetables.

Many women report valuable benefits from HRT, including increased energy levels, better glucose regulation, healthier weight maintenance, and lack of hot flashes. Some decide that the benefits of therapy outweigh the risks for them.[156] That is a decision a woman should make in conjunction with her healthcare practitioner.

Potential Adverse Effects of Estradiol Therapy[157]	
Cardiovascular	Edema, hypertension, thrombophlebitis, retinal thrombosis
Central Nervous System	Headache, depression, pain, dizziness, anxiety, migraine, nipple pain
Respiratory	Nasopharyngitis, flu-like symptoms, sinusitis, upper respiratory tract infection, headache, bronchitis, sinus congestion, pharyngitis, asthma exacerbation, cough
Dermatologic	Skin rash, pruritus, erythema multiforme, erythema nodosum, urticaria
Skeletal	Arthralgia, weakness, back and neck pain, limb pain, myalgia, leg cramps
Endocrine	Weight gain or loss, hot flash, libido changes, hirsutism, menstrual changes, porphyria exacerbation, fluid retention, hypocalcemia, elevated triglycerides, galactorrhea
Gastrointestinal	Abdominal pain, constipation, heartburn, flatulence, bloating, nausea, vomiting, diarrhea, pancreatitis, gastroenteritis, carbohydrate intolerance
Hypersensitivity	Anaphylaxis, angioedema, hypersensitivity reactions
Hepatic	Hepatic hemangioma exacerbation, jaundice
Ophthalmic	Conjunctivitis, steepening of the cornea, contact lens intolerance
Infections	Fungal and other infections
Otic	Otitis media

Contraindications to HRT

Significant medical history may be a contraindication to hormone replacement therapy. Hormone therapy contraindications include:[158] [159] [160] [161]

- ✓ Antithrombin deficiency
- ✓ Blood clots, DVT, pulmonary thromboembolism or risk of
- ✓ Breast cancer history or risk of
- ✓ Cardiovascular disease history or risk of
- ✓ Endometrial cancer history or risk of
- ✓ Endometriosis
- ✓ Genital bleeding
- ✓ Liver disease, active, with abnormal liver function tests
- ✓ Migraine with aura
- ✓ Obesity with excess lifetime exposure to estrogen
- ✓ Pregnancy
- ✓ Stroke
- ✓ Thrombophilic disorders
- ✓ Transient ischemic attack
- ✓ Vaginal bleeding of unknown origin

Bioidentical Hormone Therapy

Despite the fact that women become “deficient” in estrogen and progesterone following menopause, hormone replacement therapy comes with significant risks.

HRT using equine estrogens and synthetic progesterone had been widely used in the past. However, these hormones are not chemically identical to human hormones and have been associated with increased risk of breast cancer, dementia, cardiovascular disease, myocardial infarction, and stroke. Estrogen therapy as a standalone is associated with uterine cancer. Researchers propose that hormones structurally identical (bioidentical) to human hormones may have significant benefits with less risk:[162]

Bioidentical hormones may be available in various forms including patch, lotion, gel, spray, ring, suppository, or oral, including a combination capsule containing 100 mg of progesterone with

1 mg estradiol. Bioidenticals are available as FDA-approved formulations including compounded products. They may also be available as custom compounded products though some concerns about standardization and efficacy have been raised.[163] [164] [165]

Orally administered hormones can be rapidly metabolized by the GI tract and liver, prompting clinicians to prefer the transdermal route.[166] An early randomized controlled trial evaluated the effect of transdermal cream containing 20 mg of bioidentical progesterone from diosgenin, a Mexican yam extract. Results revealed that 25 out of 30 women reported significantly improved or completely resolved vasomotor symptoms with the transdermal cream.[167]

Optimal Takeaways

Although the phenomenon of menopause is inevitable, the symptoms and increased risk of chronic disease that accompany it may not be. A healthy lifestyle and diet along with targeted supplementation may not only help alleviate symptoms but also help reduce risk of preventable disease going forward.

The following optimal takeaways can help the clinician manage menopause safely and effectively.

- ✓ Menopause occurs in phases and usually begins between ages 45 and 52
- ✓ Alterations in menstrual cycles can be the first noticeable sign of menopause, followed by symptoms and biomarker changes
- ✓ Estrogen and progesterone regulate mitochondrial, cardiometabolic, neurological, skeletal, and reproductive functions
- ✓ Estrogen specifically
    - Reduces oxidative stress, promotes nitric oxide production, has anti-inflammatory actions, and regulates metabolic, anti-inflammatory, mitochondrial, and apoptotic genes.
- ✓ Physiological and biochemical changes associated with menopause increase risk of chronic disease and dysfunction including obesity, CVD, metabolic syndrome, depression, NAFLD, inflammation, and oxidative stress
- ✓ Monitoring biomarkers associated with menopause and cardiometabolic comorbidities would be prudent and should include
    - Estradiol, progesterone, testosterone, DHEA, SHBG, FSH, AMH, lipids, leptin, adiponectin, vitamin D, thyroid markers, inflammatory markers, homocysteine, oxidative stress markers, and bone markers
- ✓ Natural medicine, nutrition therapy, and targeted supplementation may relieve symptoms without hormone replacement therapy
- ✓ If utilized, HRT should be initiated at the lowest dose needed to resolve symptoms, especially vasomotor symptoms, and minimize systemic estrogen exposure
- ✓ Most postmenopausal women will have a serum estradiol level of 9.3 pg/mL (34 pmol/L) or less without hormone replacement therapy
- ✓ A clinical goal for estradiol of 60 pg/mL (220 pmol/L) would be required to reduce risk of osteoporosis and reduce hot flashes by 50%
- ✓ Transdermal HRT may have a better safety profile than oral estrogen
- ✓ A sustainable Mediterranean diet is recommended for reducing menopause symptoms, and reducing risk and severity of the chronic disorders that can increase during menopause
- ✓ Targeted supplementation may be needed to address micronutrient insufficiencies or increased requirements
- ✓ A trial of natural products can be implemented including black cohosh, chasteberry, evening primrose oil, isoflavones, and traditional Chinese Medicine
- ✓ Mind-body techniques may help relieve symptoms and can include cognitive behavioral therapy, hypnosis, relaxation, yoga, and mindfulness-based stress management

Additional References [168]

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