

Review Article

Menopause and Cardiovascular Implication

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Abstract

Cardiovascular disease (CVD) is one of the leading causes of morbidity and mortality in postmenopausal women.^[1] Estrogen deficiency has a negative impact on cardiovascular function and metabolism.

Key words: Menopause, cardiovascular, amenorrhea

Introduction

Cardiovascular risk factors increase with age, and in women, menopause aggravates these risk factors. Cardiovascular disease (CVD) is one of the leading causes of morbidity and mortality in postmenopausal women.^[1] Estrogen deficiency has a negative impact on cardiovascular function and metabolism.

Menopause

Menopause is diagnosed after 12 months of amenorrhea due to the loss of ovarian function. It is a physiological change, not a disease. The stages of reproductive aging workshop (STRAW) classification separate a woman's life into seven segments, with segments -2, -1, and 0 denoting the early menopausal transition, the late menopausal transition, and the final menstrual period, respectively.^[2]

Levels of follicle-stimulating hormone (FSH) >10 IU/L are indicative of declining ovarian function. FSH levels > 20 IU/L are diagnostic of ovarian failure in the peri-menopausal age group with vasomotor symptoms (VMS) even in the absence of the cessation of menstruation. FSH levels >40 IU/L done 2 months apart are diagnostic of menopause.^[3] While peri-menopause is defined as the period of 1 year after the last menstrual period. It may last for 2–8 years. It is associated with irregular menses, and fertility decreases in this period. The estimated mean age of menopause is 46.2 years in India.^[4]

Anti-Mullerian hormone (AMH), which is produced by granulosa cell of ovarian follicle, can be used to predict the

age of menopause. AMH decreases with increasing age and becomes undetectable before menopause in females. 257 normal ovulatory women, AMH, antral follicle count, and FSH were assessed and followed for 11 years. It was found that using age and AMH, the age range in which menopause will subsequently occur can be calculated.^[5] With menopause, the FSH level raises reflecting decrease in ovarian reserve and estradiol level decreases. Estrone is the major estrogen produced, which is due to peripheral aromatization of androgen produced from adrenal and ovary.

Menopausal woman may be asymptomatic or may have troublesome climacteric symptoms such as hot flashes, insomnia, headache, body ache, depression, mood changes, and weight gain. Hot flush indicates the sensation of heat, maybe associated with sweating, and sometimes followed by a chill. Onset, duration, progression, and severity of symptoms vary. The Greene Climacteric Scale, Kupperman Index, and Menopause-specific Quality of Life Questionnaire are some of the commonly used scores for menopausal symptoms. Studies on the quality of life after menopause are conflicting: Some reveal decline, while some studies show improvement, and others have no association.^[6] As the life expectancy is increasing, the duration of life spend in menopausal state is increasing, so it becomes important to address the problem associated with menopause.

There may be a link between menopausal symptoms and CVD risk. In a population-based study of 5523 women aged 46–57 years, flushing and night sweating were associated

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with higher cholesterol level, higher body mass index (BMI), and higher systolic and diastolic blood pressure compared with asymptomatic women.^[7] In wise (Women's Ischemia Syndrome Evaluation) study, 254 postmenopausal women aged more than 50 years, not taking hormone therapy, were evaluated. It was found that women with VMS <42 years had lower FMD (flow-mediated dilation), reduced endothelial function, and higher CVD mortality relative to women with later onset symptoms.^[8]

Estrogen has pleiotropic effects. It has both nuclear, slow response through regulating transcription factor and rapid non-nuclear effects through membrane-associated estrogen receptor (ER). It has a protective effect and signals through PI3K, Akt, and ERK 1/2. Estrogen decreases pathologic cardiac hypertrophy and has an anti-inflammatory property.^[9] The anti-inflammatory and antioxidant mechanism prevents plaque rupture. Estrogen increases expression of genes involved in prostacyclin synthetase and nitric oxide synthetase, increasing endothelial-derived nitric oxide and which increases in cyclic guanosine monophosphate, thereby leading to relaxation of vascular smooth-muscle cells.^[10] Estrogen therapy in postmenopausal women decreases serum total cholesterol (TC) and low-density lipoprotein (LDL) cholesterol concentrations, increases serum high-density lipoprotein (HDL) cholesterol and triglyceride concentrations, and decreases serum Lp(a) lipoprotein concentrations.

Menopause and Cardiovascular Risk Factors

Hypertension (HTN), dyslipidemia, obesity, glucose intolerance, cigarette smoking, diabetes, and sedentary lifestyle are considered as modified risk factors, whereas age, gender, and hereditary are the non-modifiable risk factors of CVDs.

Women are about 10 years older as compared to men when they develop CVDs.^[11] Menopause greatly increases the risk for coronary diseases by 3–4-fold. Women should follow a healthy lifestyle to reduce the conventional risk factors.

Age of Woman

In the wise study, the incidence of obstructive coronary artery disease in women with angina increases dramatically after the age of 50, with a prevalence of 48% in the 55–64 age group and 79% for women >75 years of age.^[8]

In population-based LifeLines Cohort Study, 63,466 women, aged between 18 and 65 years, were grouped into premenopausal, perimenopausal, naturally postmenopausal, and surgically postmenopausal. Postmenopausal women aged 45 years had higher TC and low-density lipoprotein cholesterol (LDL-c) and systolic and diastolic blood pressure than in postmenopausal women aged 50. Chronological age and menopausal status are both independently associated with CVD risk factors.^[12]

Age at Menopause

In the nurse's health study cohort, 354,326 person-years follow-up was done to access the age of menopause and impact

on cardiovascular mortality. A total of 757 incident cases of coronary heart disease (CHD) occurred with a significant association between younger age at menopause and higher risk of CHD among women who experienced natural menopause and never used hormone therapy. This increased risk was seen only with women who were current smokers but not among non-smokers and past smokers. A possible explanation is that smoking is a strong risk factor for early menopause and a strong independent risk factor for CHD and therefore a confounder.^[13]

In ladies ACS Study, 373 women with acute myocardial infarction, who underwent angiography, were asked menopause questionnaires to specifically evaluate whether the age at menopause is linked to the extent of coronary artery disease. Patients with early menopause had no differences in the extent of coronary disease at angiography, but women with late menopause had significantly better outcome during 1-year follow-up as compared with those with early menopause. With each year's delay in the menopause, the adjusted risk decreased by 12%. This study revealed that extent of the coronary disease shows a correlation with absolute age after 55 years but no correlation with the age of menopause.^[14]

Dyslipidemia

Low plasma estrogen levels may explain unfavorable lipid and carbohydrate metabolism changes rapidly occurring during menopausal transition and soon after menopause. No difference was observed in HDL, LDL, HDL:TC ratio, fasting insulin, and the ratio of fasting insulin to fasting blood glucose between women with premature ovarian failure with a mean age of 32.8 years and in those during natural menopausal transition with a mean age of 52.^[15]

HTN

Relationship between sex and prevalence of HTN is varied by world region. During earlier ages, men have a higher prevalence of HTN than women, whereas in older people, they were higher in women than in men.^[16] For every 20 mmHg systolic and 10 mmHg diastolic blood pressure increase, there is a doubling of mortality both from CHD and stroke for women and men aged 40–89 years.^[17] As compared with optimal blood pressure, high-normal blood pressure is associated with a risk factor-adjusted hazard ratio of 2.5 in women and 1.6 in men for CVD.^[18]

Obesity

It is a preventable cause of cardiovascular event. Weight gain is related to aging, menopause, lifestyle changes, and genetic factors. In both gender, central obesity increases with aging. Menopause leads to an increase of total body fat along with the redistribution of body fat from the periphery to the trunk, causing central adiposity.^[19] This is associated with insulin resistance, diabetes, and dyslipidemia.

Diabetes Mellitus

Diabetes mellitus increases the risk of CVD and its prevalence increases with aging. Diabetics mellitus (DM) prevalence is higher in older woman than man.^[20] High testosterone levels are associated with higher risk of type 2 diabetes in women but with lower risk in men, while both women and men with higher sex hormone-binding globulin (SHBG) levels have a lower risk of type 2 diabetes.^[21] There is a greater relative risk for CVD events and death from CVD in women with DM as compared to men.^[22]

Whether menopausal status independently affects the risk of developing diabetes is controversial, data from large clinical trials suggest that postmenopausal hormone therapy decreases the risk of developing diabetes mellitus. Some studies suggest that women with diabetes undergo menopause earlier than non-diabetic women,^[23] but these findings are not consistent.

A longitudinal study of 9 years in 949 participating women across the Nation SWAN (Study of Women's Health Across the Nation) revealed an increased incidence of the metabolic syndrome among perimenopausal women. Odds of developing the MetS per year in perimenopause was 1.45.^[24]

A recent study of 3639 postmenopausal women from the Rotterdam Study, a prospective cohort study, showed that women with late menopause had a significantly lower risk of type 2 diabetes. Early onset of natural menopause is an independent marker for type 2 diabetes. For each 1-year delay in the onset of menopause, the risk of type 2 diabetes decreased by 4% independent of potential risk factors for type 2 diabetes (including BMI, glucose, and insulin levels) and levels of endogenous sex hormones and SHBG.^[25]

Management of CVD Risk Factors

It is important to realize that, other than family history, many risk factors such as lifestyle, smoking diabetes, HTN, and dyslipidemia are modifiable. By stopping smoking, your risk of CVD will diminish over time. Improve in diet pattern also helps in improving the CVD risk factors.^[26] Postmenopausal females are also advised to reduce weight and performing exercise at least 30 min most days.^[27,28]

Hormone Replacement Therapy (HRT)

HRT used in menopause reduces VMS, dyspareunia, and osteoporosis. It also probably decreases the risk of type 2 diabetes and colorectal cancer. However, the use of HRT for the prevention of CHD still remains controversial. Observational studies of menopausal women taking HRT showed a reduction in the occurrence of CVD events and CHD death.

One of the largest randomized trials, Women's Health Initiative (WHI) hormone trial, a placebo-controlled study examined the effects of HRT (conjugated equine estrogens [CEE] + medroxyprogesterone acetate (MPA), or CEE

alone) on primary CVD prevention, osteoporotic fractures, and breast cancer risk. It was stopped early due to an excess of invasive breast cancer in women taking CEE plus MPA. Increased risk of CHD, stroke, and thromboembolism outweighs the benefit achieved by colorectal cancer and hip fracture reduction. All-cause mortality with hormone replacement was found to be lower when HRT was begun during the fifth decade but higher when begun after 60 years of age.^[29]

In Estrogen Replacement and Atherosclerosis (ERA) trial, 309 postmenopausal women who had angiographically verified coronary disease received either conjugated estrogen alone or conjugated estrogen plus MPA. Significant reductions in LDL-c levels and significant increases in HDL-c levels were observed; however, no change was seen in the progression of coronary atherosclerosis.^[30]

In a recent trial, Early versus Late Intervention Trial with Estradiol Trial, 643 postmenopausal women were grouped into early and late menopause according to time since menopause. After a median of 5 years, estradiol, with or without progesterone, and CIMT progression were significantly less in early postmenopause strata but not in late postmenopause strata when compared to placebo. However, no significant effect on cardiac CT measures of atherosclerosis was found in either postmenopause group.^[31]

Non-hysterectomized postmenopausal women are at increased risk of endometrium cancer if they are on estrogen-only HRT. Similarly, there is an increased risk of ovarian cancer irrespective of estrogen-only or combined estrogen-progestogen HRT.

HTN

HTN in postmenopausal female is treated in accordance to various available guidelines. While treating these patients for HTN, we should also consider for other comorbidities such as diabetes and stroke.^[32] However, the rate of hypertensive women detected, treated, and subsequently well controlled is estimated to be only 10%.^[33]

Dyslipidemias

Statin is recommended as per the current guidelines for primary prevention in women who have an elevated CVD risk.^[34] In addition, they should be prescribed to women for secondary prevention of cardiovascular events; the recommendations and targets are the same for women as for men. As mentioned previously, HRT can improve lipid profiles and lead to a reduction in LDL-c, significant increases in HDL-c, and decreases in lipoprotein(a).^[35,36]

Conclusion

The take-home message is that risk factor increases at the time of menopause and menopausal transition, some of them are due to aging and some are due to menopausal changes

itself. Doctors should be aware of these and should counsel the perimenopausal woman for screening for risk factors and cardiovascular events and for lifestyle changes and treatment if required.

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