Modulation of coronary artery disease risk factors by menopausal status: A population based study among Iranian women (KERCADRStudy)

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Original Article

Abstract

BACKGROUND: Menopause is now viewed as a risk factor for coronary heart diseases (CHD). There is a scarcity of evidence concerning the effects of menopause on coronary artery disease (CAD) risk factors. The present study aimed to evaluate the effects of menopausal status on CAD risk factors.

METHODS: The present study was designed as part of the Kerman coronary artery disease risk study (KERCADRS) that was a population-based study among a cohort of 6000 individuals aged 15 to 75 years in Kerman, Iran. Only women aged 35 to 60 years were enrolled. Participants were categorized according to reproductive age into the three groups of premenopausal, perimenopausal, and postmenopausal states.

RESULTS: The premenopausal status was accompanied with lower levels of triglyceride (TG), cholesterol, fasting plasma glucose (FPG), and blood pressure compared with the other two groups (P < 0.001). In addition, women in the postmenopausal group had higher levels of low-density lipoprotein (LDL) in comparison with the other two groups (P < 0.001). After adjusting for age, total cholesterol and LDL levels were significantly higher in the postmenopausal group compared with the other two groups (P < 0.05). In addition, total cholesterol and LDL levels, and systolic blood pressure were statistically different according to menopausal status after adjustment for both age and body mass index (P < 0.05).

CONCLUSION: The increased risk of cardiovascular disease in postmenopausal period can be explained by elevated levels of lipid profile and increased systolic blood pressure, regardless of effects of advanced age or other anthropometric parameters.

Keywords: CAD Risk Factors, Women, Premenopause, Perimenopause, Postmenopause

Introduction

Menopause is now accepted as a risk factor for coronary heart diseases (CHD) and its occurrence results in increased risk of coronary artery disease (CAD) in women.[1] This increased risk can be caused not only by estrogen deprivation, but also by its effect on lipid profile, which is likely to occur in the perimenopause period.[2] Some studies have suggested a central role for insulin in increasing CAD risk factors.[3] Moreover, menopause can be associated with the aggravation of multiple cardiovascular risk factors. These deleterious factors can be indirectly affected by treatment with estrogen and progestin combination.[4] Besides, the pointed probable mechanisms, an increase in the prevalence of CAD risk factors at the time of menopause has also been shown to be a potential risk factor for increasing CAD risk. Some studies have found high total cholesterol level, high low-density lipoprotein (LDL) cholesterol level, and high triglyceride level to be associated with menopausal status.[4-6] In addition, menopause-

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associated differences in plasma LDL cholesterol levels have been attributed to the effect of sex hormones on LDL metabolism.[7,8] However, little information is available on the effects of menopause on CAD risk factors, especially lipid levels, in large populations. The present study aimed to clarify the effects of menopausal status on various CAD risk factors and determine the situation of these risk factors in different age groups of women around menopause.

Materials and Methods

The present study was designed as a part of The Kerman coronary artery disease risk study (KERCADRS-No. 88/110).[9] The KERCADRS was a population-based, epidemiological research among a cohort of 6000 individuals aged 15 to 75 years and residences of Kerman city, Iran. The study addressed the epidemiological data regarding various coronary artery disease risk factors and menopausal status. All subjects with a history of metabolic disorders or using antilipidemic drugs were not included into the study. A well-validated questionnaire regarding risk profile was administered by trained and certified medical staff. Participants also underwent a clinical examination that included measurement of height, weight, and arterial blood pressure (mean of two measurements performed with a standard sphygmomanometer in a sitting position after a 5-min rest) according to standardized protocols. Furthermore, blood samples were taken after at least 12 h of overnight fasting and hemoglobin A_1c (HbA_1c), fasting plasma glucose (FPG), serum triglyceride (TG), and total cholesterol, and high-density lipoprotein (HDL) cholesterol were measured. LDL cholesterol was also calculated using the Friedewald formula. In this study, only women aged 35 to 60 years were enrolled. Participants were categorized according to their reproductive age into three groups of postmenopausal group (with an amenorrhea for at least 12 months),[2,10] perimenopausal group (with an amenorrhea for 6 to 12 months, or older than 40 years old with irregular bleeding, and/or older than 40 years old with regular bleeding using progesterone medication), premenopausal group (age less than 40 years with regular bleeding, or age more than 40 years with regular bleeding without using progesterone drugs, or age less than 40 years with irregular bleeding).

Lipid-lowering therapy was defined as the daily intake within the previous 15 days of at least one lipid-lowering drug among those defined by the National Guide Drug Prescription used at the time of the study.[11] Similar definitions of treatments were used for diabetes mellitus and antihypertensive treatments.[2] Hormonal treatments were defined as the daily intake of contraceptive drugs or hormone replacement therapy. Women with a history of hysterectomy were excluded. The study protocol was approved by the research and ethics committees of the Kerman University of Medical Sciences, and informed consents were obtained from all participants.

Statistical analysis

Results were presented as mean ± standard deviation (SD) for quantitative variables and were summarized by absolute and relative frequencies for categorical variables. Categorical variables were compared using chi-square test or Fisher's exact test. Quantitative variables were also compared using ANOVA, and Tukey's post-hoc analysis was used to elicit pairwise difference between means where significant differences were found. The analysis of factors associated with coronary risk factors was conducted with multivariable logistic modeling. Age and body mass index were considered as potential confounding factors. Statistical significance was determined as a P value of ≤ 0.05. All statistical analysis was performed using SPSS for Windows (version 18; SPSS Inc., Chicago, IL, USA).

Results

The mean age of the whole sample was 49.25 ± 4.61 years. Among the 1538 women, 21.0% were taking daily antihypertensive drugs, 10.9% were taking daily diabetes mellitus medication, and 13.1% were taking daily lipid-lowering drugs. Fifty women (3.3%) were currently taking hormonal replacement therapy. According to study classification, 931 women were allocated in the premenopausal group, 84 women in the perimenopausal groups, and 523 women in postmenopausal group. As presented in table 1, except for the overall prevalence of current smoking that was similar across the three subgroups, other traditional cardiovascular risk factors including family history of coronary diseases, hypertension, hyperlipidemia, and diabetes mellitus were more frequent in perimenopausal and postmenopausal groups compared to others. Systolic and diastolic blood pressures, FPG, TG, total cholesterol, and LDL cholesterol were associated with the menopausal status (Table 2). The premenopausal status was accompanied with lower levels of TG, total cholesterol, FPG, and

blood pressure compared with perimenopausal and postmenopausal statuses (P < 0.001). Moreover, women in the postmenopausal group had higher levels of LDL cholesterol in comparison with perimenopausal and premenopausal statuses (P < 0.001). After adjusting for age variable, only total cholesterol and LDL cholesterol were significantly higher in postmenopausal women compared with the other two groups. However, serum level of TG, FPG, and systolic and diastolic blood pressures were not statistically different in the different menopausal statuses. In addition, serum total cholesterol and LDL levels, and systolic blood pressure did not differ according to menopausal status.

After further adjustment for age and body mass index, postmenopausal women were importantly characterized by higher total cholesterol (P < 0.001), LDL cholesterol (P < 0.001), and systolic blood pressure (P = 0.025) compared with others (Table 1).

Discussion

The incidence of cardiovascular diseases in postmenopausal period has been estimated to be higher than 50% in some observational studies. Different physiological mechanisms are now identified which are related to the increased risk of cardiovascular disease in postmenopausal status. The beneficial effects of hormone replacement therapy on reducing risk of CAD emphasize the role of the impairment of sex hormones in triggering CAD and its-related risk factors. The major part of these deleterious effects appears to be due to an increase in total cholesterol level, LDL cholesterol level, and reduction of HDL cholesterol. Furthermore, deregulation of hormonal systems can result in endothelial dysfunction predisposing to the appearance and progression of CAD.[12,13] Besides, some other studies have shown mechanisms by which estrogen might increase coagulation or

Table 1. Comparison of cardiovascular risk factors according to menopausal status

Characteristics	Premenopausal (n = 931)	Perimenopausal (n = 84)	Postmenopausal (n = 523)	P
Family history of CAD	212 (22.8)[*]	20 (23.8)	154 (29.4)	0.005
Hypertension	89 (9.6)	15 (17.9)	117 (22.4)	< 0.001
Hyperlipidemia	69 (7.4)	17 (20.2)	138 (26.4)	< 0.001
Diabetes mellitus	14 (1.5)	3 (3.6)	18 (3.4)	0.017
Current smoking	80 (8.6)	9 (10.7)	38 (7.3)	0.384

*N (%); Comparing was performed by the ANOVA test; CAD: Coronary artery disease

Table 2. Comparison of age-adjusted means of coronary heart diseases (CHD) risk factors according to menopausal status

	Premenopausal (n = 931)	Perimenopausal (n = 84)	Postmenopausal (n = 523)	Unadjusted P	Age-adjusted P	Age and BMI adjusted P
BMI (kg/m2)	27.9 ± 4.7[*]	27.8 ± 4.6	28.5 ± 5.0	0.077	0.458	0.444
Waist circumference (cm)	85.0 ± 11.1	88.6 ± 11.0	89.2 ± 11.7	< 0.001[a,c]	0.578	0.014[c]
Systolic blood pressure (mmHg)	112.7 ± 17.3	126.0 ± 20.8	125.7 ± 20.5	< 0.001[a,c]	0.070	0.025[c]
Diastolic blood pressure (mmHg)	75.8 ± 9.5	80.6 ± 10.7	80.9 ± 10.8	<0.001[a,c]	0.186	0.073
Fasting glycemia (g/dl)	100.4 ± 34.3	113.7 ± 51.6	117.8 ± 55.2	<0.001[a,c]	0.504	0.478
Total cholesterol (mg/dl)	197.2 ± 37.9	209.3 ± 43.6	219.3 ± 47.2	< 0.001[a,c]	< 0.001[a]	< 0.001[a]
LDL cholesterol	129.1 ± 31.7	133.7 ± 32.5	144.3 ± 39.4	< 0.001[a,b]	< 0.001[a]	< 0.001[a]
HDL cholesterol	39.9 ± 10.9	39.6 ± 10.6	40.4 ± 9.2	0.663	0.791	0.788
Triglycerides	143.7 ± 79.1	167.7 ± 79.9	170.5 ± 87.9	< 0.001[a,c]	0.166	0.110

* Mean ± SD, a: P < 0.05 for postmenopausal vs. premenopausal; b: P < 0.05 for postmenopausal vs. perimenopausal; c: P < 0.05 for perimenopausal vs. premenopausal; Comparisons were performed by ANOVA test followed by Tukay's post-hoc analysis; CHD: Coronary heart diseases; BMI: Body Mass Index; LDL: Low density lipoprotein; HDL: High density lipoprotein

inflammation, which trigger coronary events in advanced lesions.[14] Animal studies have also suggested that hormones might retard early atherosclerosis, while both animal studies and human angiographic trials are conclusive that hormones do not retard progression of raised lesions.[15] It seems that these conflicting results can be caused by the different changes in the situations of CAD risk factors in postmenopausal period. Although it has been found that after adjustment for initial potential cofounders, the trend of these changes is discrepant.

In the present study on the situations of CAD risk factors in different menopausal-related periods, most of the CAD risk factors were considerably more prevalent in postmenopausal status than premenopausal and perimenopausal periods, when unadjusted for potential cofounders such as age and body mass index. However, after adjustment for these confounding indicators, the condition of some risk profiles such as anthropometric parameters, fasting blood sugar, and blood pressure changed significantly. On the other hand, regardless of the effects of age or body mass index, postmenopausal status is associated with increased levels of total serum and LDL cholesterol. Some previous studies found similar findings. In the study by Agrinier et al. after adjustment of LDL cholesterol level for age and body mass index, these parameters were still significantly higher in postmenopausal women than in premenopausal women, indicating that other factors, independent of age and BMI, strongly influence LDL cholesterol levels in women.[2] The decrease in plasma estrogen levels after menopause might play a significant role in the reduction of the clearance of LDL particles and subsequent increase in LDL cholesterol level in postmenopausal women. In this regard, estrogen replacement treatment has been shown to markedly decrease LDL cholesterol level in dyslipidemic postmenopausal women. In addition, studies in animal models have indicated that estrogen treatment is followed by a marked increase in the number of hepatic cell surface LDL receptors and a faster clearance of LDL particles.[16] Furthermore, treatment with estrogen has been shown to increase cholesterol excretion in humans, and to decrease the conversion of VLDL-apoB to LDL-apoB in rabbits.[17,18] Moreover, according to our findings, postmenopausal and perimenopausal women suffered from increased systolic blood pressure compared with premenopausal women even after adjustment for confounders. Some studies showed that elevated systolic blood pressure is a potent risk factor in premenopausal women.[19] Recent epidemiologic and experimental evidence indicate that estrogen deficiency may cause increases in systolic blood pressure through impacting endothelial vascular function and/or systemic arterial compliance.[20-23] It can be certainly intensified in postmenopausal period because of its related hormonal disturbances. However, these hypotheses should be further investigated in future studies.

Conclusion

In summary, the increased risk of cardiovascular disease in postmenopausal period can be explained by elevated levels of lipid profile and increased systolic blood pressure regardless of the effects of advanced age or anthropometric parameters.

Acknowledgements

Conflict of Interests

Authors have no conflict of interests.

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