

Association of early menopause with angiographically-derived SYNTAX score

Observational study

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Abstract

Association of early menopause with increased risk of cardiovascular events has been confirmed in previous studies. SYNTAX score (SX-score) can comprehensively quantify severity of coronary artery disease (CAD) and predict the outcomes of patients with CAD. However, the association of early menopause with SX-score has never been reported.

We prospectively included 1875 consecutive postmenopausal patients who underwent coronary angiography (CAG) and were angiographically diagnosed with CAD from January 2011 to December 2013. SX-score was calculated using the SX-score algorithm based on diagnostic angiogram. Ordinal logistic regression analysis was used to investigate the association between early menopause and SX-score.

Patients with early menopause were more likely to have a history of hypertension, diabetes, hyperlipidemia, and less likely to smoking. Besides, they have higher fasting glucose, hemoglobin A1C (HbA1c), total cholesterol (TC), low-density lipoprotein (LDL), triglyceride (TG), and body mass index (BMI) compared with the patients without early menopause. Moreover, patients with early menopause have higher SX-score and multi-vessel diseases. Ordinal logistic regression analysis showed that age, hypertension, diabetes, and early menopause exerted independent influences on SX-score. The patients undergone oophorectomy, early menopause was highly associated with SX-score.

Early menopause was an independent predictor of SX-score in postmenopausal patients with CAD.

Abbreviations: BMI = body mass index, CAD = coronary artery disease, CAG = coronary angiography, HbA1c = hemoglobin A1C, HDL = high-density lipoprotein cholesterol, LDL = low-density lipoprotein, MI = myocardial infarction, PCI = percutaneous coronary intervention, SX-score = SYNTAX score, TG = triglyceride.

Keywords: association, coronary angiography, coronary artery disease, early menopause, SYNTAX score

1. Introduction

Previous studies have shown that early menopause was associated with increased cardiovascular risk and mortality.^[1–3] The increase in cardiovascular risk by early menopause may be a consequence of estrogen deprivation^[4] or may result from a higher prevalence of cardiovascular risk factors, such as diabetes, hypertension, insulin resistance, visceral obesity, dyslipidemia, and endothelial dysfunction that occur with aging.^[5–7]

SYNTAX score (SX-score) is a comprehensive angiographic scoring system that is derived entirely from the coronary anatomy and lesion characteristics.^[8–10] It was initially designed to quantify lesion complexity. However, the value of the SX-score

to predict major adverse cardiac events (MACE) was recently validated on a series of patients undergoing percutaneous coronary intervention (PCI) for multivessel coronary artery disease (CAD)^[11–13] and/or left main disease.^[14] More recent data indicate its ability to predict periprocedural myocardial infarction (MI) in patients undergoing elective PCI.^[15] A prior research has discussed the association of early menopause with severity of CAD.^[16] However, the relationship between early menopause and SXscore has never been previously reported.

2. Materials and methods

2.1. Study population

We prospectively reviewed 1875 consecutive postmenopausal patients who underwent coronary angiography (CAG) and were angiographically diagnosed with CAD from January 2011 to December 2013. Questionnaires were used to collect information on menopause, age at menopause, reason for menopause (occurring naturally or after surgery), history of hysterectomy, oophorectomy, use of hormone therapy, hypertension, diabetes, and smoking status. Menopause was defined as cessation of menstrual periods for at least 3 years.^[17] Patients were classified as having early menopause if they experienced menopause before age 45 years.^[18] The protocol in this study was approved by the Ethics Committee of Tianjin Medical University Cangzhou Central Hospital. All cases agreed with informed consent to participate in this research. Patients who underwent estrogen replacement therapy were excluded from this study.

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2.2. Cardiovascular risk factors

After an overnight fast, blood samples of the patients were obtained at our research center. Serum levels of triglycerides (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL), low-density lipoprotein (LDL) cholesterol, fasting plasma glucose, hemoglobin A1c (HbA1c) were examined. After a 5-minute rest, seated blood pressure was calculated as the average of 2 consecutive measurements at the right brachial artery using standard mercury sphygmomanometer. Hypertension was defined as a seated systolic blood pressure (SBP) of ≥ 140 mmHg,^[19] diastolic blood pressure (DBP) of ≥ 90 mmHg, with or without treatment for hypertension. Diabetes was defined using the American Diabetes Association criteria.^[20] Patients with hypercholesterolemia were defined as those with a LDL level above 160 mg/dL or those with standard lipid-lowering therapy.^[21] Smoking history was determined by questionnaire and categorized as current, former, or never. Height (cm) and weight (kg) were measured, then body mass index (BMI) was defined as weight divided by the square of height (kg/m^2). Family history included MI, angina pectoris or sudden death.

2.3. SXscore and angiographic analysis

Under diagnostic angiogram, coronary arteries (≥ 1.5 mm) with more than 50% stenosis were scored separately and added together to provide the overall SXscore, which was calculated using the SXscore algorithm (8–10). The independent variable was supposed to be early menopause, then the control variable was non-menopause. All angiographic pertinent variables to SXscore calculation were computed by two of three experienced cardiologists who were blinded to the present study on angiograms. In the case of disagreement, the opinion of the third observer was obtained, and the final decision was made by consensus. Occluded infarct-related arteries in patients with acute MI were scored as occlusions of less than 3 months duration.

2.4. Statistical analysis

All data were processed using PASW 18.0 for Windows (SPSS, Chicago, IL). Intergroup differences of continuous variables were analyzed by ANOVA. Intergroup differences of categorical variables were compared by chi-square tests. Post-hoc tests should be performed and results of pairwise comparisons. Ordinal logistic regression was used to identify the predictors of SXscore. The effects of early menopause on SXscore were investigated in predetermined subgroups: patients with different types of menopause (natural, hysterectomy or oophorectomy). A 2-sided value of $P < .05$ was considered significantly different.

3. Results

3.1. Clinical characteristics of patients

Among the 1875 patients included in this study, the average age was 61.7 ± 9.0 years (range 40–75 years). The SXscore ranged from 0 to 50, with a mean of 15.3 ± 9.0 . Most patients with early menopause had undergone hysterectomy or oophorectomy. However, most patients without early menopause had undergone natural menopause. There were no significant differences between two groups of with and without early menopause in terms of mean age and family history of CAD. Compared with those without early menopause, patients with early menopause were more likely to have a history of hypertension, diabetes, hyperlipidemia, and less likely to smoking. Moreover, they had

Table 1

Clinical characteristics.

| Characteristic | Early menopause | | P value |
|---|------------------|------------------|---------|
| | (+) n=368 | (-) n=1507 | |
| Age mean \pm SD, years | 62.3 \pm 8.6 | 61.6 \pm 9.2 | .185 |
| Type of menopause, n (%) | | | <.001 |
| Natural | 55 (14.9) | 1336 (88.7) | |
| Hysterectomy | 188 (51.1) | 109 (7.2) | |
| Oophorectomy | 125 (34.0) | 62 (4.1) | |
| Hypertension, n (%) | 132 (35.9) | 434 (28.8) | .008 |
| Diabetes, n (%) | 133 (36.1) | 441 (29.3) | .01 |
| Hyperlipidemia, n (%) | 152 (41.3) | 510 (33.8) | .007 |
| Family history of CAD, n (%) | 60 (16.3) | 272 (18.0) | .432 |
| Smoking status, n (%) | | | .031 |
| Current | 63 (17.1) | 354 (23.5) | |
| Former | 69 (18.8) | 262 (17.4) | |
| Never | 236 (64.1) | 891 (59.1) | |
| Fasting glucose, mg/dl | 124.3 \pm 17.3 | 121.6 \pm 16.8 | .006 |
| HbA1c, % | 6.6 \pm 1.8 | 6.3 \pm 1.9 | .006 |
| TC, mg/dL | 238.7 \pm 19.2 | 233.1 \pm 17.6 | <.001 |
| LDL, mg/dL | 129.9 \pm 17.3 | 125.7 \pm 18.7 | <.001 |
| HDL, mg/dL | 52.9 \pm 9.6 | 54.0 \pm 10.2 | .061 |
| TG, mg/dL | 120.1 \pm 23.4 | 114.8 \pm 24.6 | <.001 |
| Body mass index, kg/m^2 | 25.7 \pm 2.6 | 23.2 \pm 1.9 | <.001 |
| SXscore mean \pm SD | 17.85 \pm 9.91 | 14.66 \pm 8.65 | <.001 |
| Number of diseased vessels | | | <.001 |
| 1 | 84 (22.8) | 645 (42.8) | |
| 2 | 88 (23.9) | 318 (21.1) | |
| 3 | 196 (53.3) | 544 (36.1) | |

CAD=coronary artery disease, HDL=high density lipoprotein cholesterol, LDL=low density lipoprotein cholesterol, TC=total cholesterol, TG=triglyceride; SXscore=SYNTAX Score.

higher fasting glucose, HbA1c, TC, LDL, TG, and BMI. Patients with early menopause had higher SXscore and multi-vessel diseases than the patients without early menopause (Table 1).

3.2. Comparison of parameters according to SXscore

The traditional coronary risk factors and percentage of early menopause of the studied population stratified across SXscore tertiles (≤ 9.0 , 9.0–16.0, and > 16.0) were shown in Table 2. Patients with higher SXscores were older, with higher percentage of early menopause, and more likely to have a history of hypertension,

Table 2

Comparison of parameters according to SXscore.

| Characteristic | SXlow (n=627) | SXmid (n=625) | SXhigh (n=623) | P value |
|------------------------------|------------------|------------------|-------------------|---------|
| Age, mean \pm SD, years | 58.8 \pm 8.3 | 60.5 \pm 9.3 | 65.8 \pm 9.4 | <.001 |
| Early menopause, n (%) | 98 (15.6) | 114 (18.2) | 156 (25.0) | <.001 |
| Type of menopause, n (%) | | | | <.001 |
| Natural | 491 (78.3) | 482 (77.1) | 418 (67.1) | |
| Hysterectomy | 89 (14.2) | 87 (13.9) | 121 (19.4) | |
| Oophorectomy | 47 (7.5) | 56 (9.0) | 84 (13.5) | |
| Hypertension, n (%) | 138 (22.0) | 179 (28.6) | 229 (36.8) | <.001 |
| Diabetes, n (%) | 132 (21.1) | 203 (32.5) | 239 (38.4) | <.001 |
| Hyperlipidemia, n (%) | 203 (32.4) | 212 (33.9) | 247 (39.6) | .018 |
| Family history of CAD, n (%) | 108 (17.2) | 117 (18.7) | 107 (17.2) | .718 |
| Smoking status, n (%) | | | | .141 |
| Current | 123 (19.6) | 135 (21.6) | 159 (25.5) | |
| Former | 119 (19.0) | 110 (17.6) | 102 (16.4) | |
| Never | 385 (61.4) | 380 (60.8) | 362 (58.1) | |

SXlow=SXscore ≤ 9.0 , SXmid=SXscore > 9.0 and ≤ 16.0 , SXhigh=SXscore > 16.0 .

Table 3
Predictors of SXscore in ordinal logistic regression analysis.

| Predictor | β coefficient | 95% CI | P value |
|-----------------|---------------------|-------------|---------|
| Age | 0.023 | 0.011–0.035 | .002 |
| Hypertension | 0.357 | 0.169–0.545 | <.001 |
| Diabetes | 0.503 | 0.318–0.688 | <.001 |
| Hyperlipidemia | 0.132 | 0.047–0.217 | .385 |
| Current smoking | 0.053 | 0.025–0.081 | .548 |
| Early menopause | 0.479 | 0.235–0.723 | <.001 |

CI=confidence interval.

diabetes, and hyperlipidemia, when compared with those patients with lower SXscores. Moreover, patients with higher SXscores had a higher rate of hysterectomy or oophorectomy history.

3.3. Predictors of SXscore

Among the risk factors influencing SXscore, age, hypertension, diabetes, hyperlipidemia, family history, smoking, and early menopause were examined with ordinal logistic regression analysis. The results showed that age (β coefficient=0.023, $P=.002$), hypertension (β coefficient=0.357, $P<.001$), diabetes (β coefficient=0.503, $P<.001$), early menopause (β coefficient=0.479, $P<.001$) had independent influences on SXscore (Table 3).

3.4. Association of early menopause with SXscore for subgroups of menopause

For patients who had undergone hysterectomy, early menopause was not associated with SXscore. By contrast, for those who had undergone oophorectomy, the association was even stronger (β coefficient=0.548, $P<.001$) (Table 4).

4. Discussion

In this study, we have shown that early menopause was associated with higher SX-score. This association remained significant after adjusting for age and known CAD risk factors. Moreover, the effect of early menopause on SX-score was absent in patients who had undergone hysterectomy but stronger for those who had undergone oophorectomy. This difference is consistent with the postulated biological mechanism that hysterectomy does not lead to immediate cessation of estrogen production, whereas oophorectomy does.

Estrogen deficiency is pathognomonic of the postmenopausal period.^[22,23] Consequently, the association of early menopause with SX-score could be explained by changes in the duration of exposure to endogenous estrogen.

Menopause is associated with metabolic derangements such as lipid abnormalities,^[24] visceral obesity, and insulin resistance, which are known cardiovascular risk factors. Women experienced early menopause in our study had worse metabolic profiles with an increased prevalence of diabetes, hyperlipidemia, obesity,

and insulin resistance. The reason behind these metabolic changes remains controversial because menopause is a normal consequent of aging, which is associated with an increased prevalence of cardiometabolic risk factors.^[24]

No study so far has explored association of early menopause with SX-score. However, a number of cohort studies have investigated association of early menopause with cardiovascular diseases and mortality. PRECADIW case-control study revealed that in women under 55 years old, early menopause was a very strong and independent risk marker for CAD, even stronger than most of the classical risk factors such as smoking, parental history of premature CVD, hypertension, and diabetes.^[25] The Multi-Ethnic Study of Atherosclerosis showed that early menopause predicted future CAD and stroke, while older age for menopause was independently associated with a decreased risk of incident of heart failure.^[3] Van der Schouw et al studied a cohort of 12115 postmenopausal women and showed that early menopause was associated with increased risk of cardiovascular mortality.^[11] Nasri H et al assessed relationship between premature menopause and severity of CAD.^[16] This study included 189 consecutive women with suspected CAD. Severity of CAD was classified according to the number of coronary artery stenosis, which was more than 50% in CAG. This study showed that early menopause did not predict occurrence or severity of CAD in women with suspected CAD. The small sample size and the way assessing severity of CAD in this research may lead to negative results. In our study, we assessed severity of CAD with SX-score which was derived entirely from the coronary anatomy and lesion characteristics, including the number of lesions, total occlusion, bifurcation, trifurcation, aorta-ostial stenosis, tortuosity, calcification, thrombus, diffuse lesion, and small vessel/diffuse disease.^[18,9] The results of the SYNTAX trial have demonstrated that SX-score played an important role in stratifying patients with complex CAD to aid revascularization decisions.^[12] Further evaluation of SX-score has also indicated its ability to predict clinical outcomes in patients with three vessels disease or unprotected left main disease.^[13,14] Recent study indicated that risk stratification by SX-score could be expanded to include all patients with CAD.^[26] Therefore, our study provided evidence to explain the finding that women with early menopause had an increased risk of cardiovascular mortality.

The cardiovascular effects of estrogen are direct and indirect, which could be mediated by estrogen receptor- α and estrogen receptor- β .^[5,27] The direct effects include rapid vasodilatation through increased nitric oxide production^[4,28,29] and long-term effects involving genomics-mediated changes in the expression of proteins that regulate vascular tone and response to injury.^[27,28] Estrogen-mediated genomic effects increase vasodilatory enzymes and accelerate endothelial cell growth but inhibit smooth muscle proliferation, collagen, and elastin deposition.^[27,30] Indirect effects include actions on endothelial calcium metabolism and coronary calcification, coagulation, fibrinolysis, insulin resistance, inflammation, oxidative alterations in lipids, and changes in lipid profile.^[5,27,30] Estrogen increases serum levels of HDL-C and triglycerides and decreases LDL and LDL oxidation.^[27] These effects support the cardiovascular protective role of estrogens, which is lost after the onset of menopause. External validity is the validity of generalized (causal) inferences in scientific research, usually based on experiments as experimental validity.

Interestingly, the LADIES ACS study^[31] assessed the relation between menopausal age and extent of coronary disease in postmenopausal women with an acute coronary syndrome. The

Table 4
Association of early menopause subgroup with SXscore.

| Type of menopause | n | B coefficient | 95% CI | P value |
|-------------------|------|---------------|-------------|---------|
| Natural | 1391 | 0.481 | 0.232–0.731 | <.001 |
| Hysterectomy | 297 | 0.086 | 0.097–0.075 | .386 |
| Oophorectomy | 187 | 0.548 | 0.336–0.761 | <.001 |

CI=confidence interval.

study was a multicenter prospective investigation enrolling consecutive patients aged ≥ 55 years with an acute coronary syndrome undergoing CAG. The study enrolled 675 patients, 249 men, and 426 women (mean age 74 years). Enrollment was stratified by sex (women/men ratio 2:1) and age (55–64, 65–74, 75–85, and > 85 years). Women were administered menopause questionnaires during admission. An independent core lab quantified CAD extent using the Gensini Score, which classifies both significant ($> 50\%$) and nonsignificant lesions. Linear correlation was used to appraise the association between the Gensini score and menopausal age. This study showed that menopausal age was not associated with the extent of CAD. Age at first acute coronary syndrome presentation, risk factors, and prior cardiovascular events were not affected by menopausal age.

This study used SYNTAX integration to assess the severity of coronary lesions. Our results suggest that early menopause is an independent risk factor for the severity of CAD (SX-score). The results of this study help explain the mechanisms of adverse cardiovascular outcomes in early postmenopausal patients. Patients with suspected coronary heart disease in early menopause should be actively evaluated for coronary lesions. Positive interventions are taken on patients to improve their clinical outcomes.

4.1. Limitations

There are several notable limitations to our study. First, our study has only included postmenopausal patients who were angiographically diagnosed with CAD. The results cannot be extrapolated to a general population. Second, estrogen levels were not measured at baseline. The postmenopausal period is also associated with changes in ovarian androgen predominance. Circulating androgen levels were not measured at baseline. Third, age at menopause was based on self-report, and variations in the onset and abruptness of menopause could lead to recall bias. The final limitation was that these data were collected from a single center and the sample size was relatively small.

4.2. Future directions

Further prospective multiple-center studies are required to better approve this finding.

5. Conclusion

This study demonstrated that early menopause was an independent predictor of SX-score in postmenopausal patients with angiographically diagnosed with CAD. Moreover, for those patients who had undergone oophorectomy, the association was even stronger.

Author contributions

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