Association between Age at Menopause and Postmenopausal Fasting Blood Glucose and Diabetes Mellitus: A Postprint

Authors: Luo Jiaoling, Zhang Weisen, Chai Zhihao, Zhu Feng, Zhu Tong, Jin Yali, Pan Jing, Jiang Chaoqiang, Zhang Weisen

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Abstract

Background Diabetes is a common chronic disease among postmenopausal women; however, there is limited research on whether early or delayed menopause age increases the risk of diabetes in postmenopausal women. Objective To investigate the association between early or delayed menopause age and fasting blood glucose and diabetes in naturally postmenopausal women, providing reference for diabetes prevention and control in postmenopausal women. Methods A total of 4,905 naturally postmenopausal women aged $ 50yearswereselectedfromthe"GuangzhouProspectiveCohortStudyofChronicDiseasesinMiddle−agedandElderlyPeople"toconductacross−sectionalstudyusingbaselinesurveydata.Thesurveyperiodwasfrom 54years),and397casesofdelayedmenopauseage($55 years). Generalized linear regression model results showed a linear relationship between menopause age $ 50yearsandfastingbloodglucose(= 0.024,95 $=0.019, 95%CI=-0.002~0.040, P>0.05). Compared with normal menopause age, delayed menopause age increased the risk of diabetes by 41.0% (OR=1.410, 95%CI=1.026~1.938, P<0.05), and the risk of newly discovered diabetes by 97.1% (OR=1.971, 95%CI=1.186~3.276, P<0.01). No association was found between early menopause age and the risk of diabetes (OR=0.882, 95%CI=0.612~1.273) or newly discovered diabetes (OR=0.760, 95%CI=0.410~1.407) (P>0.05). Conclusion Delayed menopause age in women is associated with increased fasting blood glucose levels and diabetes risk in postmenopausal women; no association was found between early menopause age and postmenopausal fasting blood glucose levels or diabetes. It is necessary to strengthen diabetes prevention and control measures in advance for individuals with delayed menopause age.

Full Text

The Association of Age at Menopause with Fasting Glucose and Diabetes

Jiaoling Luo[1], Weisen Zhang[1,2]*, Zhihao Chai[1], Feng Zhu[2], Tong Zhu[2], Yali Jin[2], Jing Pan[2], Chaoqiang Jiang[2]

[1]Molecular Epidemiology Research Center, the Affiliated Guangzhou Twelfth People' s Hospital of Guangzhou Medical University, Guangzhou 510620, China
[2]Team of Guangzhou Biobank Cohort Study, Guangzhou Twelfth People' s Hospital, Guangzhou 510620, China

*Corresponding author: Weisen Zhang, Chief physician; E-mail: zwsgzcn@163.com

Abstract

Background Diabetes mellitus is a common chronic disease in postmenopausal women. However, little is known about whether early or delayed age at menopause increases the risk of postmenopausal diabetes. **Objective** To explore the correlation between early or delayed age of menopause and fasting blood glucose and diabetes in natural postmenopausal women, so as to provide evidence for the prevention and control of diabetes in this population. **Methods** A cross-sectional study was conducted using baseline survey data from 4,905 postmenopausal women aged 50 and older in the Guangzhou Prospective Cohort Study on Chronic Diseases in Middle-aged and Elderly Adults. Data were collected between November 2017 and January 2020, covering demographic characteristics, socioeconomic status, lifestyle factors, medical history, and reproductive history. Physical examinations were conducted, including measurements of fasting blood glucose and blood lipid levels. The generalized linear regression (GLM) and Logistic regression models (LRM) of SPSS 28.0 were used to analyze the relationship between menopausal age and fasting blood glucose levels and diabetes. **Results** The mean age of the participants was $(60.1\$\pm5.8)years old and the mean age of menopause was (50.3\pm3.1)years. Among them, 351 women experienced ea$ $54 years), and 397 had delayed menopause(55 years). Results from GLM showed that a linear association between n$ 0.024, 95 $=0.019, 95%CI=-0.002 to 0.040, P>0.05). Comparing with the normal age of menopause, the delayed menopausal age was associated with a 41.0% higher risk of diabetes mellitus (OR=1.410, 95%CI=1.026-1.938, P<0.05) and a 97.1% increased risk of newly diagnosed diabetes mellitus (OR=1.971, 95%CI=1.186-3.276, P<0.01). In contrast, no significant associations were found between early menopause and diabetes risk (OR=0.882, 95%CI=0.612-1.273) or newly diagnosed diabetes (OR=0.760, 95%CI=0.410-1.407) (all P>0.05). **Conclusion** The delayed menopausal age is associated with an increased level of fasting glucose and risk of diabetes among postmenopausal women. However, no significant correlation was found in those with early age of menopause. It is necessary to strengthen diabetes prevention and control for

those with delayed menopausal age in advance.

Keywords: Diabetes mellitus; Age at menopause; Fasting glucose; Postmenopausal women

Introduction

Diabetes is a common metabolic disease associated with the occurrence of multiple diseases and complications. China has 129.8 million diabetic patients, and globally, the number of adults with diabetes has reached 537 million, projected to increase to 643 million by 2030. Diabetes is a prevalent chronic disease in postmenopausal women, with studies showing that women' s risk of diabetes increases after menopause, and both diabetes prevalence and related mortality are higher in women than in men. However, research on whether early or delayed menopause age is associated with diabetes remains limited and conclusions are inconsistent. Some studies suggest that both early and delayed menopause are associated with increased diabetes risk, while others find associations only with early or delayed menopause. Our previous research found that both early and delayed natural menopause age could increase obesity risk in postmenopausal women. Building on this foundation, the present study further analyzes the correlation between early or delayed menopause age and fasting glucose and diabetes to provide scientific reference for developing prevention and control measures for diabetes in postmenopausal women.

Methods

1.1 Study Subjects

This study utilized baseline data from the Guangzhou Prospective Cohort Study on Chronic Diseases in Middle-aged and Elderly Adults, a sub-project of the National Key R&D Program. The baseline survey was conducted from November 2017 to January 2020. Inclusion criteria were: Guangzhou household registration, naturally postmenopausal women aged $ $50 years, able to travel independently to the examination site at Guangzhou Twelfth People' s Hospital for questionnaire survey and free physical examination. Exclusion criteria included: history of hysterectomy, oophorectomy, or mastectomy; hormone replacement therapy; psychological or mental disorders preventing completion of the questionnaire; or unwillingness to participate. After initial screening, 5,385 eligible individuals were identified. After further excluding 480 individuals with missing data on diabetes history, treatment history, fasting glucose results, menopausal age, or covariates, the final study included 4,905 participants. This study was approved by the Medical Ethics Committee of Guangzhou Twelfth People's Hospital (Approval No. 2017002). All participants understood the study content, voluntarily enrolled, and provided informed consent.

1.2 Survey Content and Methods

(1) Questionnaire Survey: The study utilized a standardized electronic questionnaire developed based on national demonstration cohorts and the Guangzhou Biobank Cohort Study. Trained and certified research assistants (assistant nurses) conducted face-to-face interviews. Survey content included general demographic characteristics (gender, age, marital status), socioeconomic status (education level, occupation, annual household income), lifestyle factors (smoking, alcohol consumption, physical activity, dietary habits), medical history, and female reproductive history. Results were entered in real-time during the interview.

(2) Physical Examination and Laboratory Testing: Physical measurements included height and body composition. Fasting venous blood samples (3-5 mL) were collected in the morning of the examination day, centrifuged at 3,000 r/min for 10 minutes with a 15 cm radius, and serum was retained. Fasting glucose and blood lipids were measured using a cobas c311 automatic biochemical analyzer (Roche, Switzerland).

1.3 Indicator Definitions and Criteria

(1) Menopausal Age Categories: Menopausal age was categorized as early ($ 45*years*), *normal*(46 − 54*years*), *anddelayed*($55 years). **(2) Diabetes:** Included both previously diagnosed diabetes and newly discovered diabetes. Previously diagnosed diabetes was defined as self-reported physician diagnosis or diabetes treatment before baseline survey. Newly discovered diabetes was defined as no physician diagnosis before baseline survey but fasting glucose $ $7.0 mmol/L at baseline examination. **(3) Occupation:** Based on previous research, occupations were categorized as manual labor, non-manual labor, and other. **(4) Smoking and Alcohol Consumption:** Smoking status was categorized as never smoker, former smoker, and current smoker. Never smoking was defined as no smoking currently or in the past. Former smoking was defined as previous smoking but no smoking for over one year. Current smoking was defined as smoking at least one cigarette per day for more than one year. Alcohol consumption was categorized as never drinker, former drinker, and current drinker using similar definitions. **(5) Physical Activity:** Assessed using the short version of the International Physical Activity Questionnaire (IPAQ). Total metabolic equivalent (MET) values were calculated based on activity frequency and duration over the past 7 days, with physical activity intensity classified as low (<3,928 METs), medium (3,928-4,158 METs), or high (>4,158 METs).

1.4 Statistical Methods

SPSS 28.0 software was used for statistical analysis. Normally distributed continuous variables were expressed as ($\bar{x}\pm s$) and compared among groups using ANOVA. Categorical variables were analyzed using ^{2} tests. Generalized linear regression models were used to analyze the relationship between menopausal

age and fasting glucose. Multivariate Logistic regression was used to examine the effects of early or delayed menopause on diabetes. The significance level was set at α=0.05.

Results

2.1 Basic Characteristics of Study Participants

Among the 4,905 naturally postmenopausal women, the mean age was $(60.1\$\pm5.8)yearsandthemeanmenopausalagewas(50.3\pm\$3.1)$ years. There were 351 women with early menopause, 4,157 with normal menopause, and 397 with delayed menopause. No statistically significant differences were found among menopausal age groups in annual household income, smoking, alcohol consumption, dietary habits, physical activity, age at menarche, number of children, triglycerides, or low-density lipoprotein cholesterol (P>0.05). However, significant differences were observed in age, marital status, education level, occupation, years since menopause, diabetes prevalence, fasting glucose, BMI, and high-density lipoprotein cholesterol (P<0.05) .

2.2 Correlation Between Menopausal Age and Fasting Glucose Levels

To avoid the influence of glucose-lowering medications in previously diagnosed diabetic patients and to minimize reverse causality from pre-menopausal diabetes, 347 previously diagnosed diabetic patients were excluded from this analysis. Using generalized linear regression with fasting glucose as the dependent variable and menopausal age as the independent variable, and adjusting for age, marital status, socioeconomic factors [education, occupation, annual household income], lifestyle factors [smoking, alcohol consumption, dietary habits, physical activity], reproductive factors [age at menarche, number of children, years since menopause], BMI, triglycerides, HDL-C, and LDL-C, a linear relationship was found between menopausal age $\$ 50yearsandfastingglucose(= 0.024, 95 \$=0.019, 95%CI=-0.002-0.040, P>0.05).

2.3 Correlation Between Menopausal Age and Diabetes

Multivariate Logistic regression analyses were performed with diabetes status (any diabetes, previously diagnosed diabetes, or newly discovered diabetes) as dependent variables (yes=1, no=0) and menopausal age as the independent variable. Model 1 adjusted for age; Model 2 additionally adjusted for reproductive factors (age at menarche, number of children, years since menopause); Model 3 further adjusted for socioeconomic status (marital status, education, occupation, annual household income) and lifestyle factors (smoking, alcohol consumption, dietary habits, physical activity); Model 4 additionally adjusted for BMI, triglycerides, HDL-C, and LDL-C. All results showed that delayed menopausal age was associated with increased risks of diabetes and newly discovered diabetes (P<0.05) .

To ensure that newly discovered diabetes cases at baseline were indeed postmenopausal-onset, a sensitivity analysis was conducted after excluding 431 women with $ $2 years since menopause, yielding consistent results. After adjustment, delayed menopausal age was associated with increased risk of newly discovered diabetes (OR=2.209, 95%CI=1.281-3.809, P<0.01) compared to normal menopausal age, while no association was found between early menopause and newly discovered diabetes risk (OR=0.767, 95%CI=0.413-1.423).

Discussion

This study of 4,905 naturally postmenopausal women aged $ 50*years from Guangzhou communities found that d* years) and diabetes or newly discovered diabetes risk. Sensitivity analyses excluding previously diagnosed diabetic patients and women with $ $2 years since menopause yielded consistent results.

These findings align with results from China' s Jinchang Cohort Study and the U.S. Women's Health Initiative prospective cohort study, both of which found delayed menopause ($ 56*years*) *was associated with increased diabetes risk but found no association with early menop* 44*years*) *was not associated with diabetes risk*, *while later menopause*($50 years) was associated with increased risk, though that study also found very early menopause (<40 years) increased diabetes risk. The U.S. Health and Nutrition Examination Survey found only very early menopause (<40 years) was associated with increased type 2 diabetes risk. These inconsistent findings may be due to differences in study population age ranges and inclusion criteria. For instance, the China Kadoorie Biobank included individuals aged 30-79 years, while our study focused on middle-aged and elderly adults $ $50 years, and the U.S. study included postmenopausal women aged 40-79 years with hysterectomy or bilateral oophorectomy.

Ovarian aging leading to menopause and the end of reproductive life has critical effects on glucose metabolism. The ovaries are the primary source of female sex hormones, and delayed menopause indicates prolonged exposure to endogenous estrogen, typically associated with higher estrogen levels. Estrogen can elevate blood glucose by inhibiting and delaying insulin release, leading to abnormal glucose metabolism. Additionally, postmenopausal ovaries continue to produce androgens, which decline at a slower rate while sex hormone-binding globulin (SHBG) decreases simultaneously, resulting in relative androgen excess. Excess androgens further exacerbate insulin resistance and increase diabetes risk.

This study has several strengths, including a large sample size from Guangzhou communities and comprehensive adjustment for confounding effects of age, socioeconomic status, lifestyle, reproductive factors, BMI, and blood lipids, as well as sensitivity analyses focusing on newly discovered diabetes. However, limitations exist. First, self-reported menopausal age obtained through questionnaire may involve recall bias, though this is likely minimal given the distinct milestone nature of menopause. Second, the study population represents only Guangzhou residents, so caution is needed when generalizing to other regions. Third, the

number of diabetic patients with early natural menopause was relatively small in this study, warranting larger sample sizes for future exploration.

In conclusion, delayed natural menopause age is associated with increased fasting glucose levels and higher diabetes risk in postmenopausal women. We recommend enhanced diabetes prevention and control measures for women with delayed menopause, including maintaining healthy lifestyles with particular attention to sugar control and low-carbohydrate diets.

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