Association of follicle stimulating hormone and serum lipid profiles in postmenopausal women
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Abstract
The aim of the study was to observe the association between follicle stimulating hormone (FSH) levels and serum lipid profiles in postmenopausal women. A total of 411 healthy postmenopausal women with a mean age of 55 years (range 45–65 years) were enrolled in this study. Data on age, time of last menstrual period, past medical history, use of medications, and smoking status were collected, and body weight, height, and blood pressure were measured. Blood samples were collected to measure the serum concentrations of FSH, luteinizing hormone (LH), estradiol (E2), glucose, total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) using routine methods. FSH levels were negatively associated with LDL-C, even after adjustment for age, LH, E2, BMI, systolic blood pressure (SBP), and diastolic blood pressure (DBP) (OR = 0.185, 95% CI = 0.051–0.669). Although FSH may also be negatively associated with dyslipidemia (P = .06 for trend) and hypercholesterolemia (P = .079 for trend), but no statistical significance was found after adjusting for confounding factors, particularly BMI. All relevant data are within the paper and its Supporting Information files. The results indicated that lower FSH levels might increase the odds of dyslipidemia, especially the risk of LDL-C elevation, which is an important factor that increases the risk of CVD in postmenopausal women.

Abbreviations: BMI = body mass index, DBP = diastolic blood pressure, E2 = estradiol, FSH = follicle stimulating hormone, HDL = high-density lipoprotein, LDL = low-density lipoprotein, LH = luteinizing hormone, SBP = systolic blood pressure, TC = total cholesterol, TG = triglycerides.

Keywords: cardiovascular disease, follicle stimulating hormone, lipid profiles, postmenopausal women

1. Introduction
Cardiovascular disease (CVD) threatens women’s health and is the leading cause of death in postmenopausal women. Previous studies have showed that dyslipidemia is one of the most important risk factors of CVD, and after menopause, the incidence of dyslipidemia increases sharply.[1] Dyslipidemia in menopause is characterized by an increase in low-density lipoprotein (LDL) levels and a decline in high-density lipoprotein (HDL) levels.[2] These changes have a clear negative impact on the cardiovascular system, accelerating the development of CVD.[3]

Previous studies focused on the relationship between dyslipidemia and estrogen deficiency in postmenopausal women, but latest studies have found that endogenous estrogens were not independent predictors.[3] We all know that the level of estrogen is generally low in postmenopausal women, but the level of follicle stimulating hormone (FSH) is variable, especially in obese and lean women. Some studies found that hormone replace therapy (HRT) had no significant impact on lipid profiles.[4] Recent studies focus on the association between FSH and cardiometabolic factors including serum lipids, but the results are controversial whether FSH is negatively or positively associated with dyslipidemia in postmenopausal women.

So, we conducted the cross-sectional study to further observe whether changes in FSH were related to dyslipidemia in postmenopausal women. Hopefully, this will be helpful for the management of cardiovascular risk and dyslipidemias in postmenopausal women.

2. Materials and Methods
2.1. Subjects
A total of 411 healthy menopausal women between the ages of 45 and 65 who went to the Health Examination Center at Jiaxing Maternity and Child Health Care Hospital from
January 2019 to December 2020 were enrolled in the cross-sectional study. Women with amenorrhea for at least 12 months were included in the study. The exclusion criteria was as follows: FSH < 2.5 IU/L, abnormal uterine bleeding, artificial menopause, use of hormones or drugs that affect menopausal status and lipid levels within past 3 months and smoking. This study was approved by the ethics committee of Jiaxing Maternity and Child Health Care Hospital. All participants signed an informed consent form.

2.2. Data collection
The basic information including age, time of last menstrual period, past medical history, use of medications was gathered by one training doctor. Body weight, height, and blood pressure were measured using standard protocols by one training nurse. Blood samples were obtained in the morning after at least 12 hours of fasting and were tested in the laboratory of our hospital that day. Serum concentrations of FSH, luteinizing hormone (LH) and estradiol (E2) were measured using chemiluminescent immunoassays (Abbott, USA); Serum lipids concentrations were measured using an enzymatic colorimetric assay (Abbott, USA).

2.3. Definition of variables
According to the Adult Treatment Panel (ATP) III guidelines,[5] total cholesterol (TC) ≥ 6.20 mmol/L was defined as abnormal TC; Triglyceride ≥ 2.3 mmol/L was defined as abnormal triglyceride (TG); low-density lipoprotein cholesterol ≥ 4.1 mmol/L was defined as abnormal LDL-C; high-density lipoprotein cholesterol < 1.0 mmol/L was defined as abnormal HDL-C; dyslipidemia was defined as any abnormality of one or more of the four serum lipid concentrations above.

2.4. Statistical analysis
Data was analyzed in IBM SPSS Statistics 2.5 (IBM, New York). Normal distribution of data was checked using Shapiro–Wilk test. Continuous variables conforming to a normal distribution were reported as mean ± standard deviation and compared between groups by analysis of variance. Otherwise, median (interquartile range) and the nonparametric test were used. Categorical variables were reported as numbers and proportion (%). Linear regression was used to evaluate the association between FSH and lipids levels and 4 models were built to adjust for potential confounders including age and BMI. We then used multivariate logistic regression to analyze the association of FSH levels and dyslipidemia in fully adjusted models. \( P < .05 \) was considered statistically significant.

3. Results
3.1. Characteristics according to FSH quartiles in postmenopausal women
A total of 411 women participated in the study. The average age was 56.3 ± 4.5 years. The average age at menopause was 50.0 ± 3.6 years and the average menopausal period was 6.3 ± 4.7 years. The estrogen level of postmenopausal women was relatively low and stable, so we chose them as participants to reduce the impact of estrogen on the study. Participants were divided into four groups according to quartiles of FSH levels. The estrogen levels were very low in all four groups and showed no significant differences. With the increase of FSH quartiles, the levels of BMI, LH, TC, TG and LDL-C decreased gradually and the level of HDL-C increased gradually, the difference was statistically significant (\( P < .001 \)). There were also significant differences in ages, menopausal years, systolic and diastolic blood pressure (DBP) between the four groups (\( P < .05 \) (Table 1).

3.2. Association of FSH and lipids levels in postmenopausal women
In unadjusted linear regression models, FSH levels were negatively associated with TC, TG and LDL-C, and positively associated with HDL-C. After adjusting for age, LH and E2, the association with TC was attenuated but still statistically significant, yet the association with TG and HDL-C was no longer significant. In fully adjusted models, the association with LDL-C was attenuated but still statistically significant, however the association with TC was no longer significant (Table 2).

| Table 1 |
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| Characteristics according to FSH quartiles in postmenopausal women. |
| FSH range (IU/L) | Quartile 1 (n = 103) | Quartile 2 (n = 103) | Quartile 3 (n = 103) | Quartile 4 (n = 102) | \( P \) |
| ≤43.22 | 43.23-54.53 | 54.54-68.44 | ≥68.45 |
| Age (yr) | 57.46 ± 4.54 | 56.48 ± 4.52 | 56.24 ± 3.98 | 55.07 ± 4.72<.002 |
| Menopausal years (yr) | 7 (2.5) | 6 (2.1) | 6 (2.0) | 5.8 (2.6) |
| BMI (kg/m²) | 25.06 ± 3.09 | 23.54 ± 2.88<.001 | 22.59 ± 2.53<.001 | 22.20 ± 2.79<.001 |
| SBP (mm Hg) | 137.20 ± 15.47 | 130.77 ± 16.95<.001 | 129.77 ± 15.12<.001 | 129.16 ± 16.29<.001 |
| DBP (mm Hg) | 85.37 ± 9.19 | 81.15 ± 9.82<.001 | 81.50 ± 9.38<.001 | 80.63 ± 10.28<.001 |
| E2 (pg/mL) | 6.37 (6.68-8.27) | 6.11 (5.36-7.14) | 5.98 (5.31-6.66) | 5.78 (5.18-6.77) | <.001 |
| FSH range (IU/L) | 14.12 (11.81-17.96) | 19.49 | 23.58 (19.55-27.32<.001 | 31.17 (25.58-37.91<.001 |
| TC (mmol/L) | 6.16 (4.51-6.93) | 6.44 (4.17-5.99<.001 | 6.62 (3.96-5.49<.001 | 6.42 (4.23-5.23<.001 |
| TG (mmol/L) | 2.31 (1.37-2.65) | 2.00 (1.99-2.90<.001 | 1.38 (1.05-2.07<.001 | 1.51 (1.00-2.24<.001 |
| HDL-C (mmol/L) | 1.19 (1.03-1.37) | 1.28 (1.10-1.50) | 1.30 (1.07-1.48) | 1.40 (1.13-1.59<.001 |
| LDL-C (mmol/L) | 3.98 (2.77-4.46) | 2.86 (2.32-4.16<.001 | 2.79 (2.39-3.44<.001 | 2.74 (2.31-3.34<.001 |

The data are expressed as mean ± standard deviation, median (interquartile range), number (percentage) and \( P \) value was calculated by ANOVA and \( \chi^2 \) test.

BMI = body mass index; DBP = diastolic blood pressure; E2 = estradiol; FSH = follicle stimulating hormone; HDL = high-density lipoprotein; LDL = low-density lipoprotein; LH = luteinizing hormone; SBP = systolic blood pressure; TC = total cholesterol; TG = triglycerides.

aCompared with FSH quartile1 (\( P < .05 \)).
bCompared with FSH quartile2 (\( P < .05 \)).
cCompared with FSH quartile3 (\( P < .05 \)).
Table 2
Association of FSH and lipids levels in postmenopausal women.

|                | B    | SE   | 95%CI of B | Beta | P    |
|----------------|------|------|------------|------|------|
| **TC**         |      |      |            |      |      |
| unadjusted     | -0.017 | 0.003 | -0.033 to 0.009 | -0.261 | <.001 |
| Model 1        | -0.017 | 0.003 | -0.033 to 0.009 | -0.267 | <.001 |
| Model 2        | -0.016 | 0.005 | -0.027 to 0.000 | -0.250 | <.001 |
| Model 3        | -0.006 | 0.004 | -0.014 to 0.002 | -0.089 | .164  |
| **TG**         |      |      |            |      |      |
| unadjusted     | -0.010 | 0.003 | -0.016 to 0.004 | -0.163 | .001  |
| Model 1        | -0.012 | 0.003 | -0.018 to 0.005 | -0.184 | <.001 |
| Model 2        | -0.009 | 0.005 | -0.018 to 0.000 | -0.138 | .058  |
| Model 3        | -0.003 | 0.005 | -0.012 to 0.006 | -0.045 | .353  |
| **HDL-C**      |      |      |            |      |      |
| unadjusted     | 0.003 | 0.001 | 0.002 to 0.005 | 0.201 | <.001 |
| Model 1        | 0.003 | 0.001 | 0.002 to 0.005 | 0.197 | <.001 |
| Model 2        | 0.003 | 0.001 | 0.000 to 0.005 | 0.163 | .025  |
| Model 3        | 0.002 | 0.001 | -0.001 to 0.004 | 0.102 | .162  |
| **LDL-C**      |      |      |            |      |      |
| unadjusted     | -0.013 | 0.002 | -0.018 to -0.008 | -0.264 | <.001 |
| Model 1        | -0.013 | 0.002 | -0.018 to -0.009 | -0.272 | <.001 |
| Model 2        | -0.014 | 0.003 | -0.021 to -0.007 | -0.290 | <.001 |
| Model 3        | -0.007 | 0.003 | -0.013 to -0.001 | -0.139 | .034  |

Data are expressed as unstandardized coefficients (B), corresponding standard error (SE), 95% confidence interval (CI) of B, standardized coefficients (Beta), and significance (P value). Model 1 adjusted for age; Model 2 adjusted for age, LH, E2; Model 3 adjusted for age, LH, E2, BMI, SBP, DBP.

3.4. Association of FSH quartiles with the risk of abnormal lipids levels in postmenopausal women

For further observation the association between FSH and serum lipids, we performed a multivariate logistic regression with full adjustment. Comparing the highest with the lowest FSH quartile, a risk reduction of 81.5% was shown for LDL-C anomaly (OR = 0.183, 95%CI = 0.051–0.669). We also observed a slight but not statistically significant decrease in all lipids (P = .06 for trend) and TC (P = .079 for trend) compared with those in the lowest FSH quartile. No statistically significant trend association was found between FSH quartiles with TG (P for trend = 0.189) and HDL-C (P for trend = 0.117) (Table 4).

4. Discussion

The goal of the study was to find the association between FSH levels and serum lipid profiles in postmenopausal women. We found that FSH levels were negatively associated with LDL-C, even after adjustment for age, LH, E2, BMI, systolic blood pressure (SBP), and DBP. Although FSH may also be negatively associated with dyslipidemia and hypercholesterolemia, but no statistical significance was found after adjusting for confounding factors, particularly BMI. These findings suggest that lower FSH levels may increase the odds of dyslipidemia, especially the risk of LDL-C elevation, which is an important factor that increases the risk of CVD.

Following menopause, women exhibit an increased prevalence of dyslipidemia, especially high levels of LDL-C and TC, which can lead to CVD.[11] Previous studies have focused on the relationship between dyslipidemia and estrogen deficiency in postmenopausal women; however, recent studies have found that endogenous estrogens are not independent predictors of lipid levels in postmenopausal women.[13] In our study, the estrogen levels were not statistically different among the different FSH quartiles. Some studies found that HRT had no significant impact on the lipid profile, and some women still developed dyslipidemia despite HRT.[14] Other findings from large randomized trials also do not confirm the benefit of estrogen therapy for the prevention of cardiovascular disease, and HRT is not recommended for this purpose in clinical practice.[15] Clinically, we also found that by using HRT, although FSH decreased, no effect on the lipid profile was found. This phenomenon may also indicate
that low FSH levels may be a risk factor for dyslipidemia, which is consistent with previous clinical investigations. To determine whether low FSH levels had an independent association with serum lipid profiles, we classified postmenopausal women into FSH quartiles. We found that as FSH levels decreased, the levels of serum TC and LDL-C, and elevated hepatic cholesterol biosynthesis.[17] The INTERHEART study, which enrolled 52 countries worldwide, including China, showed that abnormal lipid levels are important risk factors for cardiovascular disease.[46] An assessment based on the Systematic Coronary Risk Estimation (SCORE) system of the 10-year risk of fatal cardiovascular disease suggested that LDL-C should be the optimal target in clinical practice.[20] LDL contributes to the formation of plaques, which are thick, hard deposits that can clog the arteries, thereby compromising the flexibility of arteries and resulting in atherosclerosis.[11] A previous study suggested that a reduction of LDL cholesterol by 2 to 3 mmol/L would reduce CVD risk by approximately 40% to 50%. In our study, after adjustment for full confounders, the association between FSH and LDL-C remained significantly the same as that in the unadjusted models. These findings suggest that the levels of FSH and LDL-C should be emphasized during HRT. We should use the lowest effective dose of estrogen, which could alleviate menopausal syndrome and not lower FSH to very low levels.

This study has some limitations. First, our study was only a cross-sectional observational study with a limited number of participants; second, we did not observe an association between FSH and other lipoproteins, such as apolipoprotein B and lipoprotein (a); third, the age span was not large enough and women with POI were not included.

In summary, to promote dyslipidemia management and effectively reduce the risk of CVD in postmenopausal women, studies involving different geographic regions, ethnic groups, and various lipid profiles should be conducted to determine the exact relationship and mechanism of action of FSH with serum lipids.

5. Conclusions

FSH may be associated with serum lipids in postmenopausal women; therefore, attention should be paid to FSH and LDL-C levels when HRT is administered.

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