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Original Article

Estrogen levels and risk factors for coronary artery disease in elderly women

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Abstract: Objective: To investigate the correlations between estrogen levels and the characteristics of coronary artery lesions, and risk factors for coronary artery disease (CAD) in elderly women. Methods: A total of 200 elderly women with suspected CAD admitted to Linyi Maternal and Child Health Hospital were recruited in this study and assigned to the CAD group and the non-CAD group according to the results of coronary angiography. Serum estradiol levels, lipid levels and fibrinolytic function of patients were compared between the two groups. Pearson correlation analysis was performed to explore the correlation between estradiol levels and risk factors for CAD. Results: Significantly lower estradiol levels were seen in the patients of the CAD group than those in the non-CAD group ($P<0.001$). Among the elderly women with CAD affecting one vessel, two vessels or multi vessels, those with the lowest estradiol level were found in the multi-vessel subgroup, whereas those with the highest estradiol level were in the one-vessel subgroup, and the difference was significant ($P<0.05$). Among the elderly women with various Gensini scores of coronary artery lesions, those with the highest estradiol level were found in the 0-23 scores subgroup while those with the lowest estradiol level were in the 53-188 scores subgroup, and the difference was significant ($P<0.05$). The levels of total cholesterol (TC), triglyceride (TG), low density lipoprotein cholesterol (LDL-C), plasminogen activator inhibitor-1 activity (PAI-1), and von Willebrand factor antigen (vWF: Ag), as well as fibrinogen (Fbg) concentrations in the CAD group were significantly higher than those in the non-CAD group, except that the level of plasminogen activator (t-PA) was significantly lower (all $P<0.05$). Pearson correlation analysis showed that serum estradiol levels were significantly correlated with the levels of TC, TG, LDL-C, t-PA, PAI-1 and vWF: Ag, as well as Fbg concentrations in elderly women with CAD ($P<0.05$). Conclusion: The estrogen levels of elderly women with CAD decrease more significantly than those of elderly women without CAD. More severe coronary artery lesions indicate lower estrogen levels. Estrogen levels are related to blood lipid levels and fibrinolytic status.

Keywords: Coronary artery disease, female, elderly patients, estradiol

Introduction

Coronary artery disease (CAD) has become a common cardiovascular disease that poses a great threat to human health. Previous studies tend to target at male patients, but neglect or pay no attention to female patients with CAD [1, 2]. In fact, the patterns of CAD occurrence in females are different from those of males. A study revealed that the incidence of CAD was significantly lower in premenopausal women than in male patients of the same age range, but showed an evident rising trend in postmenopausal women, though the incidence of CAD in postmenopausal women differed insignificantly from that in male patients [3]. After considering other conventional risk factors, the most critical and major difference between men and women, and between pre-and postmenopausal women, is the difference in estrogen levels. Estrogen, a steroid hormone, comprises estrone, estradiol (E2) and estriol. The above three components are different in the expression levels and functions in women. Estradiol has shown to have the most potent activity and the greatest biological effect in women; it is also the most important and active of the three [4]. In addition to its effects on the reproductive system, estrogen also plays a key role in other systems such as the circulatory system. Notably, estrogen levels might be related to the occurrence and development of CAD,

so clinicians are paying increasing attention to the effect of estrogen in elderly women with CAD.

There are currently few reports on CAD in women, especially in elderly women. A study reported a relationship between early menopausal age and the risks of CAD [5]. Compared with normal menopausal patients, the incidence of recurrent angina pectoris increased significantly in myocardial infarction patients with early menopause [6]. Early menopause is an independent risk factor for CAD [7, 8]. Reverent evidence has proved that estrogen is a protective factor for CAD and can reduce the development of atherosclerotic plaques by regulating lipid levels, vascular endothelial function, coagulation and inflammatory cytokines [9]. However, estrogen replacement therapy fails to reduce the incidence of CAD and bring no benefits in elderly women. It is noted that the association between coronary atherosclerosis and estrogen levels is complicated, and the specific association between the two needs further exploring. Therefore, this study was designed to analyze the correlation between estrogen levels and the characteristics of coronary artery lesions, lipid levels, vascular endothelial cell function, coagulation and other high-risk factors in elderly menopausal women, expecting to provide evidence for planning the strategies for early prevention and treatment of CAD in elderly women.

Materials and methods

Patients

This study was approved by the ethics committee of Linyi Maternal and Child Health Hospital, and all the participants provided written informed consent. The study recruited 200 patients with suspected CAD who had been admitted to our hospital from February 2015 to August 2016, and they underwent coronary angiography. The enrolled patients varied in age from 60 to 70 years (mean, 65.4±4.3 years). Inclusion criteria were patients older than 60 years and coronary angiography clearly showed lesions in the left main coronary artery, anterior descending artery, circumflex artery, right coronary artery and its branches; natural menopausal women; no previous coronary stent implantation or coronary artery bypass grafting; no administration of steroids, fatty acids or sulfonamides; no administration of anticoagulant agents or statin lipid-lowering drugs within the past month. Exclusion criteria were severe liver and kidney diseases, hematologic diseases, tumors, immune disorders, acute or chronic inflammatory diseases, uterine fibroids or polycystic ovary syndrome and other gynecological diseases as well as the diseases in the endocrine system; administration of estrogen or immunosuppressive agents within the past month.

Grouping method

All elderly women underwent coronary angiography using the GE Innova 3100 digital flat panel cardiac imaging system and the Judkin method. Imaging of multi-angle and multi-position was performed for visual assessment of the severity of coronary artery stenosis. At least 4 poses were projected in the left coronary artery, and at least 2 poses projected in the right coronary artery. Patients were assigned to the CAD group and the non-CAD group based on the results of coronary angiography. The patients with significant stenosis (>50%) involving the main coronary artery or its branches were assigned to the CAD group; those with coronary artery stenosis <50% or no plaque formation or stenosis were assigned to the non-CAD group [10].

Assessment of the severity of coronary artery lesions

The number of vessels with coronary artery lesions was calculated as follows: Two senior physicians reviewed the coronary angiograms; an anterior descending artery, circumflex artery and right coronary artery each was calculated as one vessel, respectively. One-vessel coronary artery lesions involved an anterior descending artery, a circumflex artery or a right coronary artery; two-vessel coronary artery lesions involved two vessels or the left main coronary artery; multi-vessel coronary artery lesions involved three vessels.

The patients were evaluated for the severity of coronary artery lesions by the Gensini scoring system [11]. The method is described in detail as follows: the products of coefficients for single lesions were calculated according to the location of coronary artery lesions: left main coronary artery lesion *5; proximal anterior descending artery *2.5; mid anterior descending artery *1.5; orifice of the circumflex artery *3.5; proximal circumflex artery *2.5; posterior left ventricular artery *0.5; the first and second

Table 1. Basic data of patients in the two groups

Factor	CAD group (n=120)	Non-CAD group (n=80)	t/χ^2	*P* value
Age (year)	64.7±5.2	65.3±5.6	0.775	0.439
Menopausal age (year)	50.1±4.3	49.5±3.9	1.003	0.317
BMI (kg/m^2)	23.4±1.3	23.6±1.5	1.002	0.318
Family history of CAD (n)	29	22	0.281	0.596
Smoking history (n)	38	30	0.728	0.394
Hyperlipidemia (n)	61	38	0.213	0.644
Diabetes mellitus (n)	47	32	0.014	0.906
Hypertension (n)	72	50	0.126	0.723

Note: CAD denotes coronary artery disease; BMI: body mass index.

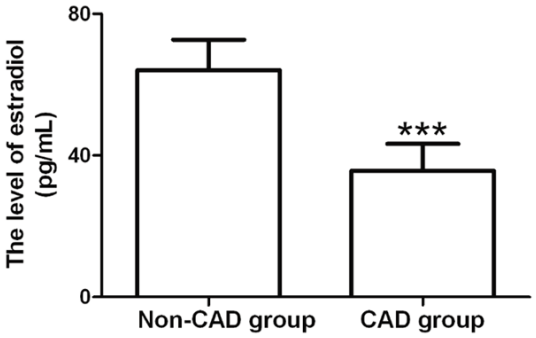

Figure 1. Comparison of estrogen levels between the two groups. Compared with the non-CAD group, ***P<0.001. CAD denotes coronary artery disease.

diagonal branches of the anterior descending artery, obtuse marginal branch and distant segment of the circumflex artery, proximal, mid, and distal segments and the posterior descending branch of the right coronary artery *1. The Gensini scores of patients were calculated in terms of the severity of coronary artery stenosis which was rated by the reduction of the area of vascular lumen: 1 point for less than 25% stenosis of the luminal diameter; 2 points for 26% to 50% stenosis; 4 points for 51% to 75% stenosis; 8 points for 76% to 90% stenosis; 16 points for 91% to 99% stenosis; 32 points for 100% stenosis or occlusion. The total Gensini scores of patients were the sum of the integrals of coronary artery lesions.

Outcome measures

Fasting venous blood was drawn from the cubital vein of each patient. The blood samples were centrifuged for 15 min at 3,000 r/min for isolation of serum. The obtained serum was stored in a refrigerator at -80°C for use. The levels of estradiol were detected using ADVIA Centaur XP, a Semi auto chemiluminescence immunoassay analyzer. Total cholesterol (TC), triglycerides (TG), low density lipoprotein cholesterol (LDL-C) and high density lipoprotein cholesterol (HDL-C) were determined by an automatic biochemical analyzer. Fibrinogen (Fbg) concentrations of patients were measured by an automatic coagulation analyzer. Chromogenic substrate assay was used to detect tissue plasminogen activator (t-PA) and plasminogen activator inhibitor-1 (PAI-1) activity. Enzyme-linked immunosorbent assay (ELISA) was used for measuring of von Willebrand factor antigen (vWF: Ag).

Statistical analysis

All data were statistically analyzed by means of the SPSS, version 21.0. Measurement data are described as mean ± standard deviation. An independent t-test was employed for comparisons between independent samples while a paired t-test was used to compare paired data, and variance analysis was used for comparisons among the three groups. Count data are described as percentages, and a chi-square test was used for between-group comparisons. The correlations between estrogen levels and the risk factors for CAD (lipid levels, measures of vascular endothelial cell function, coagulation function and fibrinolysis function) were analyzed by Pearson correlation analysis. P< 0.05 was deemed statistically different.

Results

Basic data of patients

In this study, 200 elderly female patients were enrolled; 120 cases were in the CAD group, and 80 cases were in the non-CAD group. The two groups were not significantly different in basic data including age, body mass index (BMI), family history and risk factors of CAD (**Table 1**).

Estrogen levels

The estradiol level was 64.1±8.6 pg/mL in the non-CAD group and 35.7±7.6 pg/mL in the CAD group, with significant differences between the two groups (t=24.550, P<0.001; **Figure 1** and **Table 2**).

Table 2. Estradiol levels of the non-CAD group and the CAD group

Group	Estradiol level (pg/mL)
Non-CAD group	64.1±8.6
CAD group	35.7±7.6
t value	24.550
P value	<0.001

Note: CAD denotes coronary artery disease.

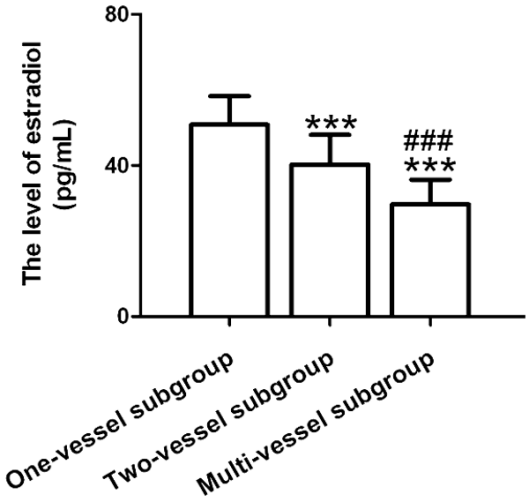

Figure 2. Comparison of estradiol levels among the one-vessel, two-vessel and multi-vessel subgroups. Compared with the one-vessel subgroup, ***P<0.001; compared with the two-vessel subgroup, ###P<0.001.

Estradiol levels of CAD patients with varied numbers of coronary artery lesions

Patients with CAD were categorized into subgroups according to the results of coronary angiography: one-vessel subgroup (n=26), two-vessel subgroup (n=28) and multi-vessel subgroup (n=66). After the patients had been matched according to their basic data, the one-vessel subgroup had 20 patients, the two-vessel subgroup had 22 patients and the multi-vessel subgroup had 58 patients. The estradiol level was 50.8±7.6 pg/mL in the one-vessel subgroup, 40.2±7.9 pg/mL in the two-vessel subgroup, and 29.7±6.5 pg/mL in the multi-vessel subgroup, with significant differences among the subgroups (F=87.080, P<0.001). Estradiol levels decreased with the increase in the number of coronary artery lesions (**Figure 2**).

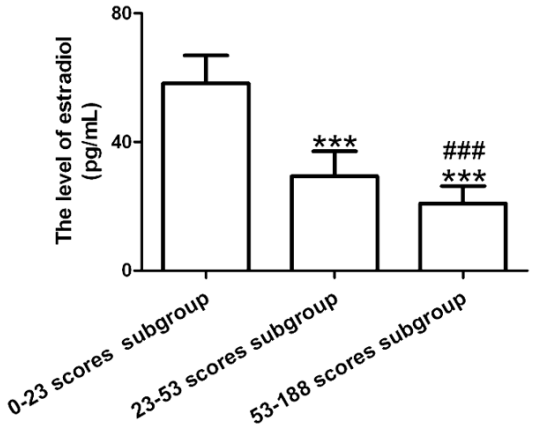

Figure 3. Comparison of the estradiol levels among CAD patients with different Gensini scores. Compared with the 0-23 scores subgroup, ***P<0.001; compared with the 23-53 scores subgroup, ###P<0.001.

Estradiol levels of CAD patients with different Gensini scores

The CAD patients were divided into subgroups of 0-23 scores (n=31), 23-53 scores (n=43) and 53-188 scores (n=46) according to the assessment criteria for coronary Gensini scores. After the patients had been matched according to their basic data, 25 cases were assigned to the 0-23 scores subgroup, 34 cases to the 23-53 subgroup and 40 cases to the 53-188 subgroup. The estradiol level was 58.2±8.7 pg/mL in the 0-23 scores subgroup, 29.4±7.7 pg/mL in the 23-53 scores subgroup, and 20.9±5.4 pg/mL in the 53-188 scores subgroup; there were significant differences among the subgroups (F=259.500, P<0.001). Estradiol levels decreased with the increase of Gensini scores in CAD patients (**Figure 3**).

Blood lipid levels of the study groups

In the patients of the non-CAD group, the levels of TC, TG, LDL-C and HDL-C were 4.1±0.9 mmoL/L, 1.6±0.7 mmoL/L, 2.3±0.5 mmol/L, and 1.1±0.4 mmol/L, respectively. In the patients of the CAD group, the corresponding values were 4.8±1.2 mmoL/L, 2.3±0.9 mmoL/L, 2.9±0.7 mmol/L and 1.0±0.3 mmol/L, respectively. The two groups differed significantly in levels of TC, TG and LDL-C (all P<0.001), but insignificantly in the HDL-C level (P>0.05; **Table 3**).

Table 3. Blood lipid levels of the study groups

Variable	Case	TC (mmoL/L)	TG (mmoL/L)	LDL-C (mmoL/L)	HDL-C (mmoL/L)
CAD group	120	4.8±1.2	2.3±0.9	2.9±0.7	1.0±0.4
Non-CAD group	80	4.1±0.9	1.6±0.7	2.3±0.5	1.1±0.5
t value		4.448	5.871	6.620	1.565
P value		<0.001	<0.001	<0.001	0.119

Note: CAD denotes coronary artery disease; TC total cholesterol; TG triglyceride; LDL-C low density lipoprotein cholesterol; HDL-C high density lipoprotein cholesterol.

Table 4. Fibrinolytic function of the two study groups

Variable	Case	vWF: Ag (%)	Fbg (g/L)	PAI-1 (AU/mL)	t-PA (IU/mL)
CAD group	120	88.9±8.2	3.8±1.5	0.8±0.2	0.4±0.1
Non-CAD group	80	78.1±7.6	2.4±1.3	0.4±0.1	0.7±0.2
t value		9.393	6.813	16.550	14.020
P value		<0.001	<0.001	<0.001	<0.001

Note: CAD denotes coronary artery disease; vWF: Ag von Willebrand factor antigen; Fbg fibrinogen; PAI-1 plasminogen activator inhibitor-1; t-PA tissue plasminogen activator.

Fibrinolytic function of the study groups

Plasma vWF: Ag, Fbg concentrations, PAI-1and t-PA were used as measures of fibrinolytic function in patients with CAD. The levels of vWF: Ag, Fbg concentrations, and the levels of PAI-1 significantly increased, but the levels of t-PA significantly decreased in the patients with CAD compared with those without CAD (P<0.001; **Table 4**).

Correlation between estrogen levels and risk factors for CAD

Pearson correlation analysis showed that estradiol levels were significantly correlated with TC, TG, LDL-C, Fbg concentrations, t-PA, PAI-1activity, and plasma vWF: Ag among elderly women with CAD. There were statistical differences (P<0.05; **Table 5**).

Discussion

CAD has become a common and frequently-occurred disease that endangers our human health. Epidemiological studies indicate that CAD is a multi-factor disease as a result of the synergistic effect of multiple risk factors [12]. Because of estrogen protection, the incidence of CAD in young women is low. With the aging of the population, however, the number of menopausal women has been on the increase, and the incidence of CAD in such population has accordingly increased dramatically. Due to atypical symptoms in menopausal women, it is difficult to make clinical diagnosis, and the rates of missed diagnosis or misdiagnosis are high [13]. There are currently only a few clinical studies on CAD in female patients, and fewer on coronary artery lesions and related mechanisms in elderly women with CAD. All these prompt us to re-recognize and consider CAD in elderly female patients and explore the causes of the disease, so as to realize early prevention and treatment.

CAD in premenopausal women is milder than that in men, but it is more severe in postmenopausal women [14]. The key disparity lies in the difference of estrogen levels. Estrogen is a fat-soluble steroid hormone, which is synthesized by aromatase catalysis of androgen [15]. In this study, estradiol, the most important type with the potent biological activity among estrogens, was selected as the representative of estrogens. Estrogen has an effect of cardiovascular protection. It can promote vasodilation by estrogen receptor via the signal transduction pathway, involve in regulating platelet function and inhibit proliferation of vascular smooth muscle as well as the expression of vascular adhesion molecules [16, 17]. However, whether elderly women benefit from the cardiovascular protection of estrogen is rarely reported.

This study showed that the estradiol levels of elderly women with CAD were significantly lower than those of elderly women without CAD; coronary artery lesions in the women were mostly multi-vessel, and severe. With the increase in the number of vessels with coronary artery lesions, the total Gensini scores became higher and the estradiol levels became lower among the elderly women with CAD, indicating that the postmenopausal changes in estrogen levels has an impact on the severity of coronary artery lesions. This is generally consistent with previous reports [18, 19].

Table 5. Correlation between estradiol levels and risk factors for CAD in elderly women

Factor	TC (mmoL/L)	TG (mmoL/L)	LDL-C (mmoL/L)	vWF: Ag (%)	Fbg (g/L)	PAI-1 (AU/mL)	t-PA (IU/mL)
Coefficient	0.253	0.284	0.292	0.511	0.469	0.541	0.570
P value	0.033	0.039	0.036	0.023	0.026	0.017	0.013

Note: TC denotes total cholesterol; TG triglyceride; LDL-C low density lipoprotein cholesterol; HDL-C high density lipoprotein cholesterol; vWF: Ag von Willebrand factor antigen; Fbg fibrinogen; PAI-1 plasminogen activator inhibitor-1; t-PA tissue plasminogen activator.

Blood lipid metabolism is closely associated with estrogen levels [20]. There is certain relationship between the occurrence and development of CAD and lipid metabolism. Clinically, lipid-regulating therapy is a decisive step in prevention and treatment of CAD. A study revealed that upregulation of the levels of TG, TC and LDL-C, and downregulation of the levels of HDL-C increased the incidence of CAD [21]. A study reported that there is a significant sex hormone disorder in elderly women with CAD, especially the significant decrease of estradiol levels, and estradiol levels are negatively correlated with the levels of TG, TC and LDL-C in the body [22]. Another study revealed that the secretion of estrogen in postmenopausal women was reduced significantly, which resulted in disturbance of lipid metabolism [23]. The correlation analysis between estradiol levels and lipid levels in this study showed that the levels of estradiol in elderly women with CAD were correlated with the measures of TG, TC and LDL-C. Hence, it is noted that a significant decrease in estradiol levels may lead to the development of CAD by affecting lipid metabolism in elderly women with CAD.

Abnormality of the fibrinolytic system is one of the important factors for the development of coronary thrombosis [24]. Damages to endothelial integrity result in decreased level of anticoagulants and increased level of pro-coagulants, leading to platelet aggregation and thrombosis. T-PA, a single-chain glycoprotein, mainly acts to degrade fibrinogen and some blood coagulation factors and inhibit thrombosis. PAI-1, a key enzyme in the fibrinolytic system, can inhibit t-PA activity and inactivate tPA. Fibrinogen can form interwoven fibrin network by thrombin action, in which leukocytes, erythrocytes and platelets are included to form thrombi. Plasma vWF: Ag not only mediates platelets to adhere to the injured sites in the vessel, but also acts as a carrier of coagulation factor VIII. Additionally, the increase in vWF: Ag is prone to hyper-coagulation and contributes to thrombosis. The results of this study demonstrated that the levels of vWF: Ag and PAI-1, and Fbg concentrations in patients with CAD were significantly higher than those in patients without CAD, while the levels of t-PA were significantly lower. Pearson correlation analysis indicated that estradiol level is correlated with tPA, PAI-1, Fbg and vWFL: Ag, suggesting that the decrease of estradiol level in elderly women with CAD leads to CAD by affecting the functions of coagulation and fibrinolysis in the body, which is similar to the results in Falcó 's report [25]. Another study reported that estrogen acted to decrease platelet adhesion and aggregation, degrade PAI-1 and reduce fibrinogen levels, which might be one of the factors for the higher incidence of postmenopausal CAD in elderly women [26]. Therefore, a significant decrease of estradiol levels may result in the development of CAD by disturbing the fibrinolytic system in elderly women with CAD.

In conclusion, estrogen was protective for CAD. More severe CAD indicated lower estrogen levels in elderly women with CAD. The protective effect of estrogen on CAD might be related to regulation of blood lipid levels and fibrinolytic function. In clinical practice, more attention should be paid to elderly women with CAD, and the risk factors for CAD should be strictly controlled to achieve early prevention and treatment. However, there are still some limitations in this study, such as single-center, and retrospective nature. Additional prospective, multicenter studies with large sample size are needed for further confirmation. Furthermore, in this study, the effect of estrogen changes on coronary artery lesions in middle-aged or elderly women is not reflected in the nature of lesions such as bifurcation, main coronary artery or calcification lesions, which is also a direction of future research.

Disclosure of conflict of interest

None.

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