Association Between Remnant Cholesterol and Carotid Atherosclerosis in Menopausal Women: A Postprint

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Abstract

Background: Carotid atherosclerosis (CAS) serves as an important indicator of preclinical manifestations of systemic atherosclerosis. Previous studies have demonstrated that elevated remnant cholesterol (RC) levels are closely associated with the pathogenesis of CAS. However, research on the correlation between RC and CAS onset in menopausal women is limited.

Objective: This study aims to investigate the correlation between RC and CAS onset in menopausal women.

Methods: A total of 307 menopausal women from Fengxiang Town, Anding District, Dingxi City, who participated in the National Stroke High-Risk Population Screening Program and underwent carotid ultrasound examination between January 2020 and October 2023, were selected as study subjects. General demographic data were collected, and carotid intima characteristics of participants were analyzed using color Doppler ultrasound. Based on the cervical ultrasound results, subjects were divided into CAS group and non-CAS group. Spearman rank correlation analysis was used to explore the correlation between RC and other risk factors for CAS onset, and multivariate Logistic regression analysis was employed to investigate whether RC is an influencing factor for CAS occurrence in menopausal women.

Results: Menopausal women in the CAS group had higher levels of age, proportion of stroke and transient ischemic attack (TIA) history, fasting plasma glucose (FPG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), RC, and pulse pressure compared to the non-CAS group ($P<0.05$). Spearman rank correlation analysis showed that RC was positively correlated with FPG and TC ($rs=0.113$, 0.280, $P<0.05$) and negatively correlated with LDL-C ($rs=-0.112$, $P<0.05$). Multivariate Logistic regression analysis revealed that high

RC level (OR=1.539, 95%CI=1.185~1.999, P=0.001), advanced age (OR=1.059, 95%CI=1.003~1.117, P=0.038), and history of stroke and TIA (OR=1.910, 95%CI=1.047~3.485, P=0.035) were risk factors for CAS onset in menopausal women. Based on the median RC value, menopausal women were divided into high RC group (RC $\geq$ 0.70) and low RC group (RC<0.70). The high RC group had higher proportions of dyslipidemia and CAS, waist circumference, BMI, and TG, and lower HDL-C compared to the low RC group (P<0.05).

Conclusion: High RC level is associated with CAS occurrence in menopausal women, and elevated RC may be an independent risk factor for CAS in menopausal women.

Full Text

Preamble

Correlation between Remnant Cholesterol and Carotid Atherosclerosis in Menopausal Women

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Abstract

Background: Carotid atherosclerosis (CAS) is a significant indicator of early systemic atherosclerosis. Previous studies have demonstrated a close relationship between elevated remnant cholesterol (RC) levels and the pathogenesis of CAS. However, limited information is available regarding the association between RC and the development of CAS in menopausal women.

Objective: To investigate the correlation between RC and the pathogenesis of CAS in menopausal women.

Methods: A total of 307 menopausal women from Fengxiang Town, Anding District, Dingxi City were selected as research subjects. These women had participated in the national high-risk stroke screening project and completed carotid artery ultrasound examinations between January 2020 and October 2023. General information was collected, and participants' carotid artery intima characteristics were analyzed using color Doppler ultrasound. Based on cervical ultrasound results, subjects were divided into CAS and non-CAS groups. Spearman

rank correlation analysis was used to explore the correlation between RC and other CAS risk factors, while multivariate logistic regression was employed to analyze whether RC is an influencing factor for CAS in menopausal women.

Results: The CAS group showed significantly higher levels than the non-CAS group in age, history of stroke and transient ischemic attack (TIA), fasting plasma glucose (FPG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), RC, and pulse pressure ($P<0.05$). Spearman rank correlation analysis indicated a positive correlation between RC and FPG as well as TC ($r = 0.113$, 0.280, $P<0.05$), while a negative correlation was observed with LDL-C ($r = -0.112$, $P<0.05$). Multivariate logistic regression analysis identified high RC levels (OR=1.539, 95%CI=1.185–1.999, P=0.001), advanced age (OR=1.059, 95%CI=1.003–1.117, P=0.038), and history of stroke and TIA (OR=1.910, 95%CI=1.047–3.485, P=0.035) as risk factors for CAS onset in menopausal women. When divided into high RC ($RC \geq 0.70$) and low RC ($RC<0.70$) groups based on the median RC value, the high RC group exhibited higher proportions of dyslipidemia and CAS, greater waist circumference, BMI, and TG levels, and lower HDL-C levels compared to the low RC group ($P<0.05$).

Conclusion: High RC levels are associated with CAS in menopausal women and may represent an independent risk factor for CAS in this population.

Keywords: carotid atherosclerosis; menopausal women; remnant cholesterol; correlation; logistic regression analysis; Dingxi City

Introduction

Remnant cholesterol (RC) refers to triglyceride-rich lipoprotein cholesterol, composed of very low-density lipoprotein and intermediate-density lipoprotein in the fasting state, and additionally includes chylomicron remnants in the non-fasting state [1]. Menopause represents a unique physiological period during which ovarian function gradually declines from robust activity to complete cessation, encompassing the perimenopausal and postmenopausal phases, generally referring to women aged 40–65 years [2]. Studies have demonstrated that menopausal women exhibit higher RC levels compared to non-menopausal women [3] and face greater atherosclerosis risk [4]. RC is closely associated with the development and progression of carotid atherosclerosis (CAS), as lipoproteins can penetrate arterial walls, leading to cholesterol accumulation in the intimal space and foam cell formation, ultimately causing CAS [1]. Clinically, increased carotid intima-media thickness and the presence of carotid plaques are regarded as ultrasonic markers of CAS [5], which represents the most fundamental pathological basis for cerebrovascular diseases [5]. Cerebrovascular diseases, characterized by high incidence, disability, and mortality rates, have become a major public health concern in China [6]. However, evidence regarding the correlation between RC and CAS in menopausal women remains scarce. This study primarily

investigates the relationship between RC and CAS in menopausal women to accurately identify high-risk individuals at early stages of CAS development, which holds significant importance for primary prevention of cerebrovascular events and optimization of treatment strategies in this population.

Methods

1.1 Study Subjects

This study utilized data from the national high-risk stroke screening project. Participants were selected from permanent residents aged 40 years and older in Fengxiang Town, Anding District, Dingxi City (those residing locally for more than six months) who participated in off-site screening at base hospitals between January 2020 and October 2023. Fengxiang Town comprises 27 administrative villages with a population of approximately 46,800, where CAS incidence is notably high.

Inclusion criteria: (1) Women aged 40–60 years; (2) Those who completed carotid artery ultrasound examinations. **Exclusion criteria:** (1) Individuals with incomplete clinical data; (2) Patients with severe infection, autoimmune disease, psychiatric disorders, malignancy, or other serious conditions. This study was approved by the Medical Ethics Committee of the Second Hospital of Lanzhou University (Approval No.: 2023A-701).

1.2 Clinical Data

Data collection included: (1) **General information:** age, height, weight, systolic blood pressure, diastolic blood pressure, etc.; (2) **Biochemical indicators:** fasting elbow venous blood samples were collected after 8 hours of fasting and analyzed using an automatic biochemical analyzer at the project base hospital laboratory to measure fasting plasma glucose (FPG), triglycerides (TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and homocysteine (Hcy); (3) **Medical history:** hypertension, diabetes, dyslipidemia (including hypercholesterolemia, hypertriglyceridemia, low HDL-C, and high LDL-C) diagnosed by secondary or higher-level hospitals; history of stroke and transient ischemic attack (TIA) determined by neurologists or diagnosed and treated at secondary or higher-level hospitals. (4) **Calculations:** RC = TC -(LDL-C + HDL-C); BMI = weight (kg)/height^2 (m^2); pulse pressure = systolic pressure (mmHg) -diastolic pressure (mmHg).

1.3 Research Methods

(1) **Data collection:** trained project personnel conducted physical examinations and laboratory tests, and collected basic information through face-to-face questionnaires. (2) **Grouping:** Participants were divided into

CAS and non-CAS groups based on CAS diagnosis; Menopausal women were further stratified into high RC (RC $\geq$ 0.70) and low RC (RC<0.70) groups using the median RC value as the cutoff.

1.4 Ultrasound Examination and CAS Diagnosis

Ultrasound examinations were performed by three sonographers with over five years of experience from the project base hospital, following the *Chinese Stroke Vascular Ultrasound Examination Guidelines* [7] strictly. Quality control was maintained through spot checks by a chief physician from the ultrasound department. Color Doppler ultrasound machines were used with conventional broadband or frequency-conversion linear array probes combined with low-frequency convex array or small convex array or sector probes. Bilateral common carotid arteries and carotid bulbs were examined, recording intima-media thickness, presence of atherosclerotic plaques, and their location, size, morphology, and acoustic characteristics. Carotid intima-media thickness $\geq$ 1.0 mm was defined as thickened carotid intima. Carotid atherosclerotic plaque was defined as a focal structure protruding into the lumen with thickness $\geq$ 1.5 mm, greater than the surrounding normal CIMT by at least 0.5 mm, or more than 50% greater than surrounding normal carotid intima-media thickness [8]. In this study, CAS included either thickened carotid intima or presence of carotid plaque.

1.5 Statistical Analysis

SPSS 26.0 software was used for statistical analysis. Normally distributed continuous variables were expressed as mean $\pm$ standard deviation and compared between groups using independent samples t-tests; non-normally distributed continuous variables were expressed as median (P_{25}, P_{75}) and compared using rank-sum tests. Categorical variables were expressed as percentages and compared using ^{2} tests. Spearman rank correlation analysis explored relationships between RC and other CAS risk factors, while multivariate logistic regression analysis investigated influencing factors for CAS in menopausal women. Statistical significance was set at P<0.05.

Results

2.1 Comparison of Clinical Data Between CAS and Non-CAS Groups

A total of 307 menopausal women were enrolled, including 130 cases (42%) in the CAS group and 177 cases (58%) in the non-CAS group, with a mean age of (53.5$±$4.8) years. The CAS group exhibited significantly higher levels of age, history of stroke and TIA, FPG, TC, LDL-C, RC, and pulse pressure compared to the non-CAS group (P<0.05). No significant differences were observed between groups in BMI, proportions of hypertension, dyslipidemia, or diabetes, nor in TG, HDL-C, or Hcy levels (P>0.05) .

2.2 Spearman Rank Correlation Analysis

Spearman rank correlation analysis revealed that RC was positively correlated with FPG and TC (r =0.113, 0.280, P<0.05) and negatively correlated with LDL-C (r =-0.112, P<0.05). No significant correlations were found between RC and age or pulse pressure (r =0.087, 0.850, P>0.05).

2.3 Multivariate Logistic Regression Analysis of CAS Influencing Factors

Using CAS occurrence (assignment: yes=1, no=0) as the dependent variable, variables with P<0.05 from Section 2.1 [RC (assignment: actual value), FPG (assignment: actual value), age (assignment: actual value), pulse pressure (assignment: actual value), history of stroke and TIA (assignment: yes=1, no=0) (Note: Considering the RC calculation formula, TC and LDL-C were not included simultaneously with RC in the analysis)] were entered as independent variables into multivariate logistic regression analysis. The results showed that high RC levels, advanced age, and history of stroke and TIA were risk factors for CAS onset in menopausal women (P<0.05) .

When menopausal women were divided into high RC (RC $\geq$ 0.70) and low RC (RC<0.70) groups based on the median RC value, the high RC group demonstrated significantly higher proportions of dyslipidemia and CAS, greater waist circumference, BMI, and TG levels, and lower HDL-C levels compared to the low RC group (P<0.05) .

Discussion

Our findings are consistent with previous research. A study by QIAN et al. [11] found that elevated fasting RC levels were significantly associated with subclinical CAS. WANG et al. [12] conducted a prospective cohort study based on Chinese adults, monitoring RC levels over nine years in 3,976 individuals who completed carotid ultrasound examinations, and found that RC accumulation and variability were independently associated with CAS risk. Although the exact mechanisms linking RC with CAS remain unclear, several potential biological pathways may be involved. First, remnant lipoproteins can penetrate arterial walls and accumulate in the intima due to their resistance to degradation, contributing to foam cell and plaque formation [13]. Second, elevated RC levels play a significant role in promoting endothelial vasomotor dysfunction, and changes or activation of endothelial function represent early events in atherosclerosis development [14]. Additionally, RC can induce expression of pro-atherothrombotic molecules in endothelial cells through redox-sensitive mechanisms [15]. Finally, cholesterol retained in the intimal space can activate the immune system, leading to low-grade inflammation [16], which VARBO et al. [17] identified as a risk factor for atherosclerosis. These findings collectively

demonstrate that RC plays an important role in CAS pathogenesis, and our study further confirms that menopausal women with high RC levels may face increased CAS risk.

Previous studies have rarely examined the relationship between RC and CAS risk specifically in menopausal women. Our research expands current understanding of the RC-CAS relationship by demonstrating that high RC levels constitute an independent risk factor for CAS in menopausal women. Additionally, we identified advanced age and history of stroke and TIA as potential risk factors for CAS in this regional menopausal population.

According to National Bureau of Statistics data, in 2020, Chinese women aged over 40 years numbered 34.86 million, accounting for 50.65% of the female population. CAS prevalence increases steadily with age and is concentrated primarily in rural areas [9]. With extended female life expectancy, most women experience menopause, a transitional period lasting considerable duration. Menopausal women frequently exhibit adverse changes in metabolic biomarkers, including increased very low-density lipoprotein, intermediate-density lipoprotein, LDL, and LDL-C levels, along with reduced LDL particle size—recognized risk factors for CAS [10]. To date, LDL-C reduction has served as the cornerstone of preventive CAS treatment; however, analysis of clinical trial data reveals substantial residual risk even when LDL-C is controlled at optimal levels [11]. CAS is closely related to cerebrovascular disease development [5], and despite recent progress in CAS prevention and management in China, the prevalence remains concerning. As discussed, menopausal women may face higher CAS risk, making early identification of risk factors critically important for primary prevention of cerebrovascular disease in this population.

Our observation of RC levels in menopausal women with different CAS statuses revealed that elevated RC represents an independent risk factor for CAS. Furthermore, Spearman correlation analysis suggested that menopausal women with high RC and CAS may have higher FPG levels ($r = 0.113$, $P < 0.05$). Although RC was positively correlated with TC ($r = 0.280$, $P < 0.05$) and negatively correlated with LDL-C ($r = -0.112$, $P < 0.05$), these relationships cannot be interpreted as indicating high TC and low LDL-C levels in menopausal women with CAS and high RC, as these correlations may result from the RC calculation formula. Additionally, compared to menopausal women with low RC levels, those with high RC exhibited higher CAS incidence, dyslipidemia prevalence, BMI, waist circumference, and TG levels, along with lower HDL-C levels.

Advanced age and history of stroke and TIA have long been recognized as established risk factors for CAS [18,19]. Therefore, relevant authorities should implement strict RC level control in menopausal women in this region, maintaining them at optimal levels. Targeted primary prevention strategies for CAS should be enhanced for elderly populations, with increased health education and improved primary prevention strategies specifically for menopausal women with advanced age and history of stroke and TIA. These measures are crucial for reducing CAS risk and alleviating the cerebrovascular disease burden in this

region.

RC values are easily obtained through standard lipid profiles without requiring additional resources, making them readily calculable and suitable for widespread clinical application to identify high-risk menopausal women for early CAS detection. The baseline characteristics of our analyzed data were similar to those of original study participants, suggesting minimal selection bias. However, several limitations should be acknowledged. First, this cross-sectional study has limited capacity to establish causal relationships between RC and CAS. Second, the relatively small sample size and geographic restriction to northwest China may limit generalizability. Finally, the lack of follow-up data on cerebrovascular events prevents prospective investigation of baseline RC' s impact on acute vascular events following CAS. Clearly, future large-scale, multicenter prospective studies are needed to further confirm the association between RC and CAS in menopausal women.

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