Association Between Blood Lipid Profiles and Atrial Fibrillation: A Case-Control Study

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Background: Dyslipidemia is the most frequent comorbidity in patients with cardiovascular disease. However, studies examining the relationship between blood lipid profiles and AF have produced inconsistent results.

Material/Methods: A total of 651 patients were enrolled into 3 groups: Healthy controls (n=64), Paroxysmal AF (PAF; n=270), and Continuous AF (CAF; n=317). All enrolled patients underwent routine baseline 12-lead electrocardiography (ECG) and 24-h dynamic ECG along with blood testing, which included the following: complete metabolic panel, hepatic function, renal function, circulating thyroxine, fasting high-density lipoprotein cholesterol (HDL -C), low-density lipoprotein cholesterol (LDL-C), triglycerides (TG), and total cholesterol (TC).

Results: Patients with AF had significantly higher levels of triglycerides (TG), lower levels of LDL-C-c, and lower levels of HDL-C ($p<0.05$). TC (OR 0.979, $p<0.9247$) and TG (OR 0.945, $p<0.6496$) were negatively and linearly associated with PAF, while TG (OR 0.807, $p=0.2042$), LDL-C (OR 0.334, $p=0.0036$), and HDL-C (OR 0.136, $p=0.0002$) were negatively and linearly associated with CAF.

Conclusions: Compared to healthy controls, patients with AF had lower blood lipid levels, especially LDL-c and HDL-c levels. Hypolipoproteinemia may increase patient susceptibility to developing AF.

MeSH Keywords: Atrial Fibrillation • Cholesterol, LDL • Triglycerides

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Background

The annual prevalence of atrial fibrillation (AF) has steadily increased over the past 75 years, especially in the younger population. By 2050, the overall prevalence of AF is expected to triple that which was observed in 2006 [1]. In addition, the incidence of AF-related ischemic stroke has tripled for patients ≥80 years of age over the past 25 years despite the introduction of anticoagulants; these numbers are expected to triple again by 2050.

Improved prevention strategies for AF and its sequelae remain an important global public health priority [2]. Studies have shown that age, sex, obesity, cardiovascular disease, and diabetes mellitus are closely related to the occurrence of atrial fibrillation [3,4]. Dyslipidemia is a major contributor to the development of atherosclerosis and coronary heart disease, both of which are closely related to the development of AF. High levels of low-density lipoprotein cholesterol (LDL-C) and low levels of high-density lipoprotein cholesterol (HDL-C) are also closely associated with the eventual development of coronary artery disease [5]. The role of dyslipidemia in the development of other cardiac conditions, such as atrial fibrillation (AF), is less clear. Few longitudinal studies have been published on this topic, and these studies have produced inconsistent results [6–9]. One prior study found that chronically elevated plasma concentrations HDL-C may increase the risk of AF [10]. The purpose of the present study was to investigate the relationship between blood lipid profiles and the corresponding increased risk of AF.

Material and Methods

Study population

This prospective study was approved by the Ethics Committee of Anzhen Hospital and informed consent was obtained from each patient. Patients with AF who were admitted to Anzhen Hospital between October 2016 and May 2017 and who met the inclusion criteria were eligible. We excluded patients with a history of cerebrovascular accident (CVA), trauma, or prior surgery within 3 months before admission, as well as those who had an acute infectious disease within 2 weeks before admission or within the first week of hospitalization. All patients underwent blood testing for hepatic function and renal function to determine final inclusion; patients with liver enzymes greater than 3 times the normal reference values or with creatinine >130 mmol/L were excluded from the study.

A total of 651 patients were enrolled into 3 groups: Healthy controls (n=64), Paroxysmal AF (PAF; n=270), and Continuous AF (CAF; n=317). Healthy controls were defined as either being disease-free or with slight hyperlipidemia. PAF was defined as AF occurring within the past 7 days with at least 48-h intervals of sinus rhythm. CAF was defined as persistent and permanent AF without conversion to sinus rhythm. All enrolled patients underwent routine baseline 12-lead electrocardiography (ECG) and 24-h dynamic ECG.

Statistical analyses

Statistical analyses were performed using the SAS Software Package (Version 9.2, Statistical Analysis System, SAS Institute Inc., Cary, NC). Comparisons between categorical variables were performed using χ^2 tests [11]. Comparisons between continuous variables were performed using analysis of variance (ANOVA) or the Wilcoxon rank-sum test [12]. Analysis of covariance (ANCOVA) was used to accommodate differences in age and sex between each group; [12] these data are presented as arithmetic means ± standard error. While controlling for age and sex, a logistic regression model was utilized to assess potential relationships between different blood lipid profiles and the subsequent development of AF (data are presented along with 95% confidence intervals or standard errors). The relative contributions of independent variables on the development of PAF were assessed using a stepwise logistic regression model [13]. Multiple logistic regression analysis was also performed to calculated odds ratios (along with their corresponding 95% confidence intervals or standard errors) while simultaneously controlling for age, sex, and the presence or absence of hypertension [13]. All p-values are two-tailed, where a value of less than 0.05 represented statistical significance unless indicated otherwise.

Results

Baseline characteristics

Table 1 summarizes the baseline demographics of each study group (Healthy Controls, PAF, and CAF). Overall, healthy controls were younger, were more often female, had lower blood sugar, and lower systolic blood pressures than the PAF and CAF groups (p<0.05). Patients in the PAF and CAF groups also had significantly higher levels of triglycerides (TG), lower levels of LDL-C-c, and lower levels of HDL-C (p<0.05).

Table 2 summarizes the clinical characteristics of patients within the PAF and CAF groups. Overall, the patients in the CAF group were more often smokers, had larger left atria, and had lower ejection fractions (P<0.05).

Clinical outcomes

Table 3 summarizes the results of logistic regression analyses of the relationships between individual clinical characteristics and the

Table 1. Subject baseline characteristics.

	Overall (n=651)	Heathy person (n=64)	PAF (n=270)	CAF (n=317)	P-value
Age(SD)	59.4±11.1	49.6±7.2	61.2±10.8	59.1±11.1	<.0001
Sex, male (%)	395 (60.5)	16 (25)	158 (58.5)	221 (69.7)	<.0001
BMI kg/m^2 (SD)	27.±20.5	25.0±3.8	27.0±21.6	28.3±22	0.4893
SBP mmHg (SD)	125.±17.6	116.6±14.1	129.±18.0	124.±15.8	<.0001
DBP mmHg (SD)	78.5±11.8	77.2±9.8	78.0±11.9	79.3±12.1	0.2467
TC (mmol/L) (SD)	4.6±1.0	4.7±0.7	4.6±1.1	4.6±1.1	0.4088
TG (mmol/L) (SD)	1.4±0.9	1.1±0.4	1.4±0.7	1.5±1.1	0.0093
LDL-C (mmol/L) (SD)	2.8±0.9	3.0±0.5	2.8±0.9	2.7±0.9	0.0391
HDL-C (mmol/L) (SD)	1.3±0.4	1.6±0.7	1.3±0.4	1.2±0.3	<.0001
GS (mmol/L) (SD)	5.9±0.4	5.1±0.8	6.0±1.4	6.0±1.6	<.0001

BMI – body mass index; weight (kg)/height (m)^2; SBP – systolic pressure; DBP – diastolic blood pressure; TC – total cholesterol; TG – triglyceride; LDL-C – low-density lipoprotein cholesterol; HDL-C – high-density lipoprotein cholesterol; GS – blood glucose; PAF – paroxysmal atrial fibrillation; CAF – continuous atrial fibrillation.

Table 2. Baseline characteristics of PAF and CAF.

Characteristics	Overall (N=587)	PAF (n=270)	CAF (n=317)	P-value
Smoking (%)	128 (22.0%)	44 (16.5%)	84 (26.7%)	0.0033
Drinking (%)	178 (22.0%)	82 (30.7%)	96 (30.4%)	0.9309
Coronary heart disease (%)	73 (12.6%)	35 (13.3%)	36 (11.4%)	0.504
High blood pressure (%)	290 (49.6%)	148 (55.4%)	141 (44.6%)	0.0093
Diabetes (%)	81 (13.9%)	40 (15.0%)	40 (12.7%)	0.4255
Cerebral infarction (%)	75 (12.9%)	33 (12.5%)	42 (13.4%)	0.755
Hyperlipemia (%)	169 (29.5%)	82 (31.2%)	86 (27.9%)	0.3947
White blood cell (G/L) (SD)	6.5±2.4	6.4±2.3	6.6±2.5	0.3708
Neutrophile granulocyte (%)	60.9±8.9	61.2±8.4	60.6±9.3	0.3515
Hypersensitivity to thyroxin(miu/L) (SD)	2.6±3.0	2.7±3.3	2.5±2.7	0.5883
Glycosylated serum albumin (%)	14.3±2.7	14.3±2.5	14.4±2.8	0.6969
C-Reactive Protein (mg/L) (SD)	2.0±3.1	2.1±3.4	1.9±2.8	0.4975
Left atrial anterior and posterior diameter(mm) (SD)	40.7±5.4	38.6±4.7	42.5±5.3	<.0001
Ejection fraction (%)	62.1±7.8	64.1±6.5	60.3±8.4	<.0001
Creatinine (Cr umol/L) (SD)	73.4±21.0	73.6±25.5	73.3±15.9	0.8639

CAD – coronary heart disease; HBP – high blood pressure; DM – diabetes; CI – cerebral infarction; WBC – white blood cell; NE – neutrophile granulocyte; LA – left atrial anterior and posterior diameter; EF – ejection fraction; Cr – creatinine.

Table 3. Multiple logistic regression analysis of AF risk factors and accompanying odds ratios (OR) and 95% confidence intervals (CI) for TC or TG or LDL-C and HDL-C after adjusting for age, sex, body mass index, systolic pressure, diastolic blood pressure, and blood glucose.

	B	SE	P	OR	Lower CI	Upper CI
TC (mmol/L)	0.707	0.373	0.058	2.028	0.976	4.213
TG (mmol/L)	0.171	0.3281	0.6023	1.186	0.624	2.257
LDL-C (mmol/L)	−1.1775	0.3869	0.0023	0.308	0.144	0.658
HDL-C mmol/L)	−1.3125	0.5163	0.011	0.269	0.098	0.74

Table 4. Multiple logistic regression analysis of PAF risk factors and accompanying odds ratios (OR) and 95% confidence intervals (CI) for TC or TG or LDL-C and HDL-C after adjusting for age, sex, body mass index, systolic pressure, diastolic blood pressure, and blood glucose.

	B	SE	P	OR	Lower CI	Upper CI
TC (mmol/L)	−0.0209	0.2206	0.9247	0.979	0.636	1.509
TG (mmol/L)	−0.057	0.1253	0.6496	0.945	0.739	1.208
LDL-C (mmol/L)	0.112	0.2433	0.6452	1.119	0.694	1.802
HDL-C mmol/L)	0.0898	0.2542	0.724	1.094	0.665	1.8

Table 5. Multiple logistic regression analysis of CAF risk factors and accompanying odds ratios (OR) and 95% confidence intervals (CI) for TC or TG or LDL-C and HDL-C after adjusting for age, sex, body mass index, systolic pressure, diastolic blood pressure, and blood glucose.

	B	SE	P	OR	Lower CI	Upper CI
TC (mmol/L)	1.002	0.3693	0.0067	2.724	1.321	5.617
TG (mmol/L)	−0.2145	0.1689	0.2042	0.807	0.58	1.124
LDL-C (mmol/L)	−1.0977	0.3768	0.0036	0.334	0.159	0.698
HDL-C mmol/L)	−1.9977	0.5431	0.0002	0.136	0.047	0.393

presence or absence of AF (irrespective of the type of AF). LDL-C (OR 0.308, p=0.0023) and HDL-C (OR 0.269, p<0.011) were negatively and linearly associated with AF irrespective of the type of AF.

Tables 4 and 5 summarize the results of logistic regression analyses according to the presence or absence of PAF and CAF, respectively. TC (OR 0.979, p<0.9247) and TG (OR 0.945, p<0.6496) were negatively and linearly associated with PAF, while TG (OR 0.807, p=0.2042), LDL-C (OR 0.334, p=0.0036), and HDL-C (OR 0.136, p=0.0002) were negatively and linearly associated with CAF.

Discussion

Our results showed that low serum levels of LDL-C and HDL-C were present in patients with AF, irrespective of the type of

AF. For PAF, low serum levels of TC and TG were found, whereas low serum levels of TG, LDL-C, and HDL-C were found in patients with CAF. These findings suggest that hypolipoproteinemia may be an independent risk factor for both PAF and CAF.

It is well-established that increased plasma concentrations of TC and LDL-C, especially when combined with reduced levels of HDL-C, are significant risk factors for cardiovascular disease [14–17]. Our results are contrary to well-established norms, and we believe this discrepancy is related to the effects of thyroid dysfunction on both lipid profiles and sinoatrial (SA) node conduction [18,19]. When compared to the euthyroid state, plasma levels of TC and LDL-C have been shown to be increased in hypothyroidism and decreased in hyperthyroidism. The alternating levels of LDL-C and apo B observed in thyroid disorders may result from predictable fluctuations in LDL-C receptor activity [18,19]. Our results corroborate these

past findings and also shed light on the possible pathophysiology involved in determining whether patients develop PAF or CAF; specifically, circulating thyroxine was found to be decreased in CAF, but the levels of LDL-C and HDL-C were found to be higher in PAF.

The relationship between the presence of dyslipidemia and subsequent development of AF is still controversial, however [7,20–23]. In a cross-sectional study, patients with PAF were found to have reduced levels of circulating TC, TGs, and HDL-C levels when compared to those without AF, although no direct comparisons were made specifically between PAF and CAF [20]. In another study, patients with AF were found to have lower levels of TC than those without AF, although no differences in plasma concentrations of HDL-C were found between groups [7]. A separate study found no statistically significant relationships between blood lipid levels and the presence or absence of AF [8]. In a large Japanese cohort, lower HDL-C levels were found to be strongly associated with an increased tendency to develop AF, and this association was strongest in females. In addition, the investigators found that TC and LDL-C levels were negatively correlated with AF [21]. In 2 large community-based cohorts, high TGs and low HDL-C were associated with a higher risk of AF after accounting for relevant clinical risk factors and biomarkers. In contrast to previously published studies, they found that neither LDL-C and total cholesterol were associated with the prevalence of AF [22]. In a previous population-based prospective study, no independent association between HDL-C or TG levels and the prevalence of AF were found, whereas lower levels of LDL-C and TC were associated with an elevated risk for AF. The investigators also found no independent associations between lipid-lowering medications (such as statins) and the relative risk of AF [23]. A recent study showed that patients with AF had lower levels of TC, LDL-C, and HDL-C than those not developing AF, and found that low HDL-C levels predict new AF [24]. Another recent study found a negative correlation between the total number of LDL and VLDL particles and AF [25]. A study suggested that in post-menopausal women, atrial fibrillation could be promoted by the association of CETP B2B2/AA genotype with higher triglycerides values. The results of these recent studies are similar to our study [26].

Factors such as advancing age, female sex, obesity, metabolic syndrome, and hypertension are well-documented risk factors for the development of AF, suggesting that a strong link may exist between atherosclerosis and AF [10,27]. In our study, blood lipid levels, especially LDL-C levels, were negatively associated with cardiovascular diseases, although these relationships were found to be the opposite in AF. There are several possible mechanisms to explain this phenomenon. Firstly, epidemiologic studies have demonstrated significant increases in the prevalence of AF with increasing age [1], while other studies have found that blood lipid levels generally decrease in patients older than 60 years. A separate study reported that increasing age and decreasing blood lipid level may result in AF because of left atrial enlargement, abnormal SA node conduction, and degeneration of the myocardium [28]. Secondly, hyperthyroidism is a well-known independent risk factor for AF. Thyroxine stimulates cholesterol synthesis by inducing HMG-CoA activity, promotes liver cholesterol breakdown, and eventually lowers circulating levels of LDL-C. Thirdly, a previous study confirmed that chronic inflammation and oxidative stress are also important risk factors for AF [29]. Lipoproteins (HDL-C and LDL-C) can be anti-inflammatory, particularly against bacterial endotoxins within the systemic circulation [7,8,29,30]. Fourthly, because low plasma levels of HDL-C have been shown to predispose to hypertrophic cardiomyopathy [31–34], and therefore AF, abnormally low baseline levels of HDL-C may have indirectly produced an increased risk of AF due to structural changes in the atria rather than changes in lipid profiles. Fifthly, the inverse association between LDL-C levels and AF has been attributed to the stabilizing effect of cholesterol on myocardial cell membranes, which may impact ion channel density and function and other aspects of membrane excitability [35–37]. Another prospective study with 23 738 healthy subjects found that the negative correlation between LDL-C and AF is also found in other atherogenic lipoproteins, suggesting that these correlations are unlikely to be mediated by direct cholesterol effects [25]. There are several causes that could explain inconsistent results between studies, such as lack of adjustment for confounding risk factors, differences in population and regional characteristics, and the choice of covariables in models.

Limitations

The present study has several limitations. First, it is possible that differences in sample size, geographic region, research design, and other confounding factors related to our specific study population may have produced results that contrast with prior studies. Second, only patients with PAF and CAF underwent complete metabolic panels (including thyroxine levels and C-reactive protein) and cardiac ultrasound measurements of left atrial dimensions and ejection fractions; therefore, comparisons could not be made between AF and the healthy controls with respect to these particular variables.

Conclusions

When compared to healthy controls, patients with AF had lower blood lipid levels, especially LDL-c and HDL-c levels. Hypolipoproteinemia may increase patient susceptibility to developing AF.

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