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Atherogenic index of plasma is positively associated with the risk of all-cause death in elderly women

A 10-year follow-up

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Summary
Background The blood concentrations of total cholesterol and low-density lipoprotein (LDL) do not predict survival in patients older than 60 years. The atherogenic index of plasma (AIP) is a logarithm of the triacylglycerol to high-density lipoprotein (HDL) ratio and a surrogate for the concentration of small dense LDL. It might be a better reflection of the risk of all-cause death in elderly patients.
Methods We conducted a prospective observational study of patients with arterial hypertension older than 60 years. The concentrations of total cholesterol, LDL, HDL and triacylglycerol were measured at the time of the recruitment and the patients were observed for 10 years. Cox regression analysis was performed to assess the effects of lipoproteins and AIP on survival.
Results A total of 500 patients were recruited and 473 of them (226 men, 247 women) either died or successfully completed the 10-year follow-up and were included in the analysis. The AIP was positively associated, while HDL concentration was negatively associated with the risk of all-cause death adjusted for age, smoking habits, statin use, history of diabetes mellitus, myocardial infarction, stroke and peripheral artery occlusive disease (PAOD) in elderly women but not in men. The LDL, total cholesterol, triacylglycerol and non-HDL concentrations were not associated with the risk of death in both sexes.
Conclusions The AIP is positively associated with the risk of all-cause death in elderly women with arterial hypertension independent of age, smoking habits, statin therapy and comorbidities.

Keywords Atherogenic index · HDL · LDL · Risk of mortality · Elderly population

Abbreviations

AIP	Atherogenic index of plasma
BMI	Body mass index
CAD	Coronary artery disease
CVD	Cardiovascular disease
HDL	High-density lipoprotein
LDL	Low-density lipoprotein

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TAG Triacylglycerol
VLDL Very low-density lipoprotein

Introduction

Despite improvements in their treatment and prevention, cardiovascular diseases (CVDs) remain a leading cause of death in European countries [1]. The majority of CVDs are found in patients older than 60 years [2]. There is a large body of evidence connecting dyslipidemia involving high concentrations of low density lipoprotein (LDL) and low concentrations of high density lipoprotein (HDL) with the development and progression of CVD [3–6]. Elderly patients represent a very difficult population for the assessment of cardiovascular risk because of multimorbidity and the effects of numerous confounding factors. Some evidence indicates that LDL and total cholesterol concentrations are not predictors of mortality in the geriatric population, suggesting the existence of a J-shape rather than a linear relationship [6–8]. A recent meta-analysis revealed a negative association between LDL concentration and mortality in patients over 65 years. The authors even questioned the validity of the cholesterol theory in elderly patients [9]; however, this contradicts the strong evidence from prospective randomized statin trials and may, therefore, not be an indicator of the lack of negative impact of LDL on the elderly population but a consequence of various confounding factors [5, 6]. After recognizing the roles of LDL and HDL as strong cardiovascular risk factors, several markers that can be calculated from the concentrations of lipoprotein fractions were developed in an effort to more accurately predict cardiovascular mortality and morbidity. The most promising markers were the non-HDL cholesterol (non-HDL) concentration and the atherogenic index of plasma (AIP). There is clear evidence that non-HDL, which is calculated as the total concentration of cholesterol minus the LDL concentration, is a strong predictor of CVD morbidity, and its predictive value even exceeds that of LDL [10, 11]; however, the true value of the AIP, which is the logarithmic transformation of the triacylglycerol (TAG) to HDL ratio, is yet to be determined. Dobiášová and Frohlich pointed out the association between increased AIP and low LDL particle size for the first time. They postulated that the AIP is a surrogate for small dense LDL particles [12]. This lipoprotein subfraction is well-known for its strong association with the development of coronary artery disease (CAD), and it predicts all-cause mortality [13–16]. Later, Dobiášová et al. further supported their theory that AIP is strongly associated with atherosclerosis and its complications by establishing an association between the AIP and coronary angiographic findings in patients with CAD [17]. In a prospective study by Onat et al. AIP was even identified as an independent predictor of CVD morbidity [18] and a meta-analysis of 15 studies proved that the AIP predicts the risk of development of type 2 diabetes mellitus better that traditional lipid markers [19]. To our knowledge, the relationship between AIP and survival in the geriatric population has never been studied; therefore, our goal was to assess the association between AIP and all-cause mortality in the elderly population and to determine if it might pose a better prognostic value in the elderly.

Methods

Patients and design

We conducted a prospective observational study of a population of patients with arterial hypertension at the 2nd Department of Internal Medicine, University Hospital of Bratislava. Patients older than 60 years were consecutively selected from all outpatients and inpatients between 2006 and 2007. At the time of recruitment, demographic and anthropometric data, pharmacotherapy and comorbidities were collected. Arterial hypertension was defined as documented resting systolic arterial blood pressure of at least 140 mm Hg and/or diastolic blood pressure of at least 90 mm Hg. Plasma LDL, HDL, total cholesterol and TAG concentrations of fasting venous blood (at least 12 h of fasting) were examined. Patients with a history of oncologic diseases except long-term remission (at least 5 disease-free years), liver cirrhosis, Cushing syndrome, corticotherapy, uncontrolled hypothyroidism or hyperthyroidism, chronic kidney disease requiring renal replacement therapy, ethyl alcohol and drug abuse, and malabsorption syndrome were excluded. The survival rate or date of death was assessed 10 years after recruitment from the official national database of the Health Care Surveillance Authority of the Slovak Republic, which contains exact dates of death.

Blood sampling and processing

Blood was sampled from the cubital vein using a vacutainer set. The blood samples were kept at room temperature for 30 min and subsequently the supernatant was separated by centrifugation for 10 min at 3,000 rpm. The supernatant was stored at 4 °C and processed within 8 h of sampling.

Biochemical analyses

Total cholesterol, LDL, HDL, and TAG concentrations were determined by an enzymatic colorimetric method (Cobas Mira Plus, Roche Diagnostics, Montclair, NJ).

Statistical analysis

The descriptive data were provided as mean ± standard deviation. The means of the quantitative vari-

ables were assessed using the T-test (for normal distribution) and Mann-Whitney test (for abnormal distribution). Normal distribution was verified using the Kolmogorov-Smirnov test. The proportional difference between categorical variables was compared using the χ^2-test. The associations between LDL, HDL, non-HDL, TAG, AIP and survival were evaluated by multivariate Cox regression analysis using age, smoking habit, statin use and history of diabetes mellitus, myocardial infarction, peripheral artery peripheral artery occlusive disease (PAOD) and stroke as confounding factors. *P*-values less than 0.05 were regarded as significant.

Ethics

All patients provided informed consent and approved the use of their medical records and data from registries for the study purposes. The study was conducted in accordance with the ethical principles of biomedical research of the declaration of Helsinki. The study was approved by the ethical committee of the Faculty of Medicine, Comenius University, Bratislava.

Results

A total of 500 patients were recruited and 473 of them (226 men, 247 women) who died (the dates of death were recorded) or successfully completed the 10-year follow-up were included in the analysis. Of the patients 27 were lost to follow-up because they moved out of the country (lost to national database). The basic characteristics of the study patients are presented in Table 1. Men had significantly higher AIP, lower HDL and TAG, and mean survival. Among the men, there were significantly higher proportions of myocardial infarction and type 2 diabetes mellitus (Table 1). There were significantly more deaths in the male patients (Table 1). There was a trend of more statin use among women; however, the difference did not reach statistical significance (Table 1).

Regression analysis

By employing multivariate Cox regression analysis, using age, smoking habit, history of diabetes mellitus, myocardial infarction, stroke and PAOD, and statin treatment as confounding factors, we found that AIP was positively associated with all-cause mortality in women but not in men (Table 2). In women, all-cause mortality was significantly negatively associated with HDL concentration (Table 2). The LDL, non-HDL, total cholesterol and TAG concentrations were not significantly associated with mortality (Table 2).

Discussion

The association between lipoprotein concentration and CVD risk has been studied by numerous authors for decades, and total cholesterol and LDL are well known cardiovascular risk factors [3–6]; however, the relationship between LDL and mortality in elderly patients is now a subject of vigorous debate, with many authors questioning its usefulness and predictive value [6, 8]. This prospective observational study demonstrates that AIP is a usable predictive marker of all-cause mortality in a high-risk elderly female population. Among all lipoprotein markers, only AIP was positively associated with all-cause mortality but only in women and independent of age, smoking habit, statin use, history of diabetes mellitus, myocardial infarction, stroke and PAOD. The AIP was developed as a marker of increased cardiovascular risk that might possess better prognostic value than total cholesterol, LDL and HDL concentrations. The background of

Table 1 Basic characteristics of the study population

	Men ($n = 226$)	Women ($n = 247$)	*P*-value
Age (years)	72.17 ± 8.678	73.93 ± 9.118	0.341
BMI (kg/m^2)	27.22 ± 6.470	27.50 ± 5.366	0.644
Survival (months)	61.05 ± 45.609	74.68 ± 42.510	<0.05
TAG (mmol/l)	1.39 ± 0.679	1.53 ± 0.826	<0.05
Cholesterol (mmol/l)	4.17 ± 1.100	4.71 ± 1.218	0.210
LDL (mmol/l)	2.52 ± 0.843	2.74 ± 0.916	0.428
HDL	1.03 ± 0.340	1.26 ± 0.479	<0.05
Non-HDL (mmol/l)	3.14 ± 1.220	3.44 ± 1.127	<0.05
AIP	0.11 ± 0.270	0.07 ± 0.326	<0.05
Myocardial infarction (%)	27.2	13.4	<0.001
PAOD (%)	17.1	15.5	0.63
Diabetes mellitus (%)	44.2	34.0	<0.05
Stroke (%)	16.4	13.8	0.78
Statin use (%)	28.8	33.2	0.07
Death (%)	65.5	46.6	<0.05

AIP atherogenic index of plasma, *BMI* body mass index, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein, *P-value* probability, *PAOD* peripheral artery occlusive disease, *TAG* triacylglycerol

Table 2 Cox regression analysis of effects of lipoprotein markers on survival adjusted for history of diabetes mellitus, myocardial infarction, PAOD, smoking, age and statin use

	Gender	*P*-value	Exp(B)	95% CI
AIP	Men	0.801	1.087	0.570–2.072
	Women	<0.05	2.149	1.160–3.984
TAG	Men	0.806	1.031	0.809–1.313
	Women	0.527	1.087	0.839–1.408
LDL	Men	0.997	1.000	0.812–1.232
	Women	0.730	0.954	0.731–1.180
HDL	Men	0.475	1.223	0.704–2.125
	Women	<0.05	0.555	0.351–0.878
Non-HDL	Men	0.744	1.028	0.869–1.217
	Women	0.556	0.945	0.782–1.141
Cholesterol	Men	0.638	1.040	0.883–1.226
	Women	0.152	0.869	0.717–1.053

AIP atherogenic index of plasma, *CI* confidence interval, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein, *PAOD* peripheral artery obstructive disease, *TAG* triacylglycerol

this theory is that AIP is a surrogate for concentration of atherogenic small dense LDL particles [12, 17]. There is a large body of evidence connecting dense LDL concentration with increased cardiovascular risk [13–15]. Small dense LDL particles are more prone to oxidation and LDL with oxidized apoprotein B is regarded as highly atherogenic [20]. Small dense LDL concentration is also associated with the expression of adhesion molecules on endothelial cells; thus, it is linked to endothelial dysfunction [21]. Dobiasova and Frohlich demonstrated that AIP inversely correlates with LDL particle size in a high diversity population composed of both high and low-risk individuals with high correlation coefficients [12].

The theory of small dense LDL as a factor connecting AIP with mortality in the elderly is supported by the findings of Toft-Petersen et al. They conducted a cross-sectional study which found an association between small dense LDL concentration and the presence of CAD in the elderly population, which was verified by coronary angiography [14]. Another study verified that apolipoprotein B, which increases with decreasing LDL size, is a better predictor of CVD mortality in patients over 70 years [22]. Vascular dementia, which might significantly contribute to increased mortality in the geriatric population, is also associated with higher small dense LDL concentrations and lower mean LDL diameter [23]. On the other hand, a study by Goliasch et al. failed to prove any association between small LDL particle concentrations and the risk of premature myocardial infarction, but positive associations with large and medium LDL were shown; however, their population consisted of relatively young patients (40 years or less) [24]. The AIP is a function of TAG concentration. High TAG concentrations might, therefore, serve as a harmful element connecting AIP with mortality. A study by Bathum et al. found a positive association between TAG and CAD mortality in elderly women between 50 and 60 years old. Also, the highest TAG quartile in both sexes was found in individuals older than 60 years. Furthermore, they did not find any association between LDL and mortality in both sexes [25]. The mean LDL diameter is strongly negatively associated with TAG. The VLDL particles and chylomicrons rich in TAG interact with LDL particles in a reaction catalyzed by cholesterol ester transfer protein. This reaction leads to the formation of TAG-enriched LDL particles, which are precursors of small dense LDL [26]; however, in our study, there was no association between TAG and mortality. In patients older than 60 years, Bathum et al. [25] found an association only in the quartile with the highest TAG. We were unable to assess the quartiles separately due to the fewer number of patients. In order to show that small dense LDL are behind the association between AIP and less favorable survival, future studies directly measuring small dense LDL and LDL particle size in the geriatric population are needed.

Another factor linking the AIP with mortality risk might be a low HDL concentration as AIP decreases with increasing HDL. In contrast to LDL, HDL concentration does not change with age and remains relatively stable throughout [27]. In our population, survival decreases with decreasing HDL concentration in women. This is consistent with the findings of Weverling-Rijnsburger et al. who found that HDL concentration, not LDL concentration, is the predictor of CAD and stroke mortality in old age. Low HDL even predicted the risk of death from infection independent of comorbidities [28]. Another study found an association between low HDL and stroke risk in the elderly [29]. A cross-sectional study by Zuliani et al. found a relationship between low HDL and dementia [30]. The fact that HDL is the only lipoprotein fraction connected to mortality risk in the elderly population indicates that low HDL might be behind AIP and mortality relationship; however, it is not known if the HDL concentration is a true risk factor or just a marker of increased risk in the population of geriatric patients.

Just like previous studies, we were unable to find any connection between all-cause mortality and LDL,

total cholesterol and non-HDL [6–8]; however, we do not assume that this lack of association translates to a lack of harmful effects of LDL on atherosclerosis progression in this population but more likely to the effect of polymorbidity and of many confounding factors that are more prominent in older age. This conclusion is based on the effectiveness of statins in the elderly, which has been proved by many trials [6]. Low HDL in the elderly is associated with relatively low LDL and total cholesterol concentrations [31]. If low HDL is the marker of increased mortality in the elderly, low HDL might be the significant confounding factor behind the lack of association between total cholesterol and mortality.

In men, we were unable to find any lipoprotein predictor of all-cause mortality, despite the higher mortality in this group. We assume that this was caused by higher morbidity among male patients. There was a significantly higher prevalence of diabetes mellitus and a significantly higher proportion of men had a history of past myocardial infarction; therefore, we assume that these comorbidities contributed to high mortality in the cohort of men. Possibly more men died as a consequence of diabetes complications and coronary atherosclerosis already developed at the time of recruitment; therefore, death independent of current lipoprotein status might have been more frequent. Multivariate analysis was not able to neutralize the effect of such strong confounders. Further studies with equal morbidity among sex groups are needed to confirm if AIP is associated with mortality in elderly men.

According to our findings, AIP might serve as a future economic and accessible lipoprotein marker of increased cardiovascular risk in elderly populations. Accessibility is its main advantage compared to direct measurement of small dense LDL concentration, which is technically much more demanding. Aa association of AIP with mortality in the elderly also highlights the importance of further studying the role of small dense LDL, TAG and TAG-rich particles and low HDL in the pathogenesis of atherosclerosis and its complications in the elderly.

Limitations

Because of the study design, we were unable to assess the causes of death of our participants. For this reason, we were unable to measure the effects on CVD mortality; however, we do not consider it a serious flaw of our data, because all-cause mortality is regarded as the hardest endpoint even in studies in the field of cardiology [31].

We used diabetes mellitus and statin use as the covariates in the Cox regression analyses because we regarded them as possible confounding factors; however, because of the study design, only diabetes diagnosed and statin treatment prescribed at the time of the recruitment were taken into consideration.

We did not include history of CAD as a confounding factor in the regression analysis because of the known high level of underdiagnosis of CAD in our elderly population (elderly patients are unwilling to undergo ergometric test or coronary angiography).

Conclusion

The atherogenic index of plasma is positively associated, while HDL is negatively associated with the risk of all-cause death adjusted for age, statin therapy, smoking habits and history of diabetes mellitus, myocardial infarction and PAOD in women older than 60 years. Since AIP correlates with small dense LDL concentration, low mean LDL size might contribute to atherosclerosis progression in elderly women.

Compliance with ethical guidelines

Conflict of interest M. Bendzala, P. Sabaka, M. Caprnda, A. Komornikova, M. Bisahova, R. Baneszova, D. Petrovic, R. Prosecky, L. Rodrigo, P. Kruzliak, and A. Dukat declare that they have no competing interests.

Ethical standards All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

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