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# The Interconnection of Metabolic Disorders and Carotid Atherosclerosis in the Kazakh Population<sup>1</sup>

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### Abstract

**Background:** The mortality rate of cardiovascular disease (CVD) exceed mortality rates of other causes. Atherosclerosis (AS) as a result of chronic inflammation underlies death caused by CVD. Metabolic disorders are signs of AS. We studied the interconnection of metabolic disorders and carotid atherosclerosis in the Kazakh population.

**Methods:** The 399 Kazakh patients with AS participated in the study. The participants were divided into two groups according to levels of low-density lipoprotein (LDL), triglycerides (TG), and body mass index (BMI). Differences in the median value of glucose, lipid profile, white blood cells, uric acid, and BMI were studied in these groups.

**Results:** Lipid profile indicators were significantly higher in the 2<sup>nd</sup> group ( $p < 0.001$ ), which was divided based on LDL. In groups divided on TG and BMI basis, indicators of white blood cells, BMI, high-density lipoprotein, TG, glucose, uric acid, LDL, and total cholesterol ( $p < 0.05$ ) were higher than in the 2<sup>nd</sup> group. The number of plaques (3 and more) was 4.15% more among men than women. Lipid parameters were directly correlated with the number of plaques. The probability of occurrence of plaques increased with a high content of TG and BMI

**Keywords:** cardiovascular disease; atherosclerosis; plaque; dyslipidemia; obesity.

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( $p < 0.05$ ).

**Conclusions:** With hypertriglyceridemia and overweight, inflammatory processes and metabolic disorders proceed markedly. Dyslipidemia causes an increase in plaques in carotid arteries. Obesity and lipid profile parameters are specific prognostic markers for AS.

## INTRODUCTION

The prevalence of cardiovascular disease (CVD) and associated costs continue to increase. CVD is known as the leading cause of death. It takes the lives of 17.7 million people annually, which is 31% of all deaths worldwide (World Health Organization, 2017).

In fact, atherosclerosis (AS) as a consequence of a chronic inflammation underlies death from CVD.

AS is a variable combination of changes in endarterium, including accumulation of lipids, complex carbohydrates, fibrous tissue, blood components, calcification, accompanied by changes in tunica media (Sergienko, Ansheles, & Kukharchuk, 2017). AS usually begins at a young age and remains asymptomatic until late life. Some researches showed that among predominantly different locations of AS, AS of common carotid artery (CCA) is one of the most significant prognostic predictors of CVD and mortality (Bhatt, 2006; U-King-Im, Young, & Gillard, 2009). Such AS sequelae as myocardial infarction and stroke, caused by spontaneous atherothrombotic occlusion, represent the most common cause of death worldwide (Herrington, Lacey, Sherliker, Armitage, & Lewington, 2016; Kruk et al., 2018).

AS treatment is an important step towards the proper treatment and prevention of CVD (Hirata et al., 2018; Kirichenko et al., 2020). Therefore, early detection and treatment of patients with an atherosclerotic plaque in the carotid artery might contribute to CVD prevention.

Thickening of the intima-media complex (IMC) of CCA for 0.1 mm is connected with increased risk of stroke and myocardial infarction of 18% and 15% respectively (Lorenz, Markus, Bots, Rosvall, & Sitzer, 2007). Therefore, it is imperative that effective interventions aimed at improving arterial health are determined.

Lipid profile includes levels of total cholesterol (TC), triglyceride (TG), high-density lipoproteins (HDL), low-density lipoproteins (LDL). It plays a key role in the pathophysiology of CVD and is an important modifiable risk factor for CVD progression (Kawai et al., 2013). Lipid accumulation are considered to be key processes of atherosclerosis development (Poznyak et al., 2020). Several index indicators reflecting atherogenic to antiatherogenic lipoprotein ratio is also used in clinical practice for integral characterization of blood plasma lipid spectrum. The simplest and at the same time highly informative indicator is the cholesterol atherogenic coefficient (AC). The coefficient is calculated based on the determination of TC and HDL cholesterol. CA value is a sensitive indicator in predicting the risk of developing atherosclerotic cardiovascular heart disease (Çakırca, 2018).

Some studies showed that the lipid profile was significantly associated with the presence and size of carotid plaque (Hou, Li, Gao, & Tian, 2018; Luo, Li, Guan, & Xu, 2014; Wang et al., 2010; Yang et al., 2014; Zhang et al., 2012). On the contrary, according to the crossover study in Algeria, a lower level of HDL was connected with a higher prevalence of AS of CCA, but not LDL (Abi-Ayad, Abbou, Abi-Ayad, Behadada, & Benyoucef, 2018). A study

conducted in the USA did not find a significant association between HDL and the number of carotid artery plaques (Gardener, Morte, Elkind, Sacco, & Rundek, 2009). The discrepancy may exist due to many factors, including a heterogeneous population of the study, different regions of the study, and different research plans.

As emphasized in the literature, plenty of factors play a key role in the occurrence of AS in addition to lipid profile. These factors are obesity (Recio-Rodriguez et al., 2012), an increase in white blood cells (Gerhardt & Ley, 2015), uric acid (Arévalo-Lorido, Carretero-Gómez, & Robles Pérez-Monteoliva, 2019; Song et al., 2019), and glucose (Katakami, 2018).

The chance of CVD progression is associated with an unhealthy diet, excessive consumption of sodium and processed foods, animal products, low consumption of fruits and vegetables, as well as lack of exercise, overweight and obesity, stress, alcohol, and smoking (Anand et al., 2015). Some scientific evidence suggests that healthy eating may be one of the preventive factors for the death of CVD (Mozaffarian & Ludwig, 2010) and may even reverse heart disease (Lacroix, Cantin, & Nigam, 2017).

The population of Kazakhstan consumes a large amount of animal products and carbohydrates and also does not receive fiber, micro and macro elements in the required amount (Shakiyeva et al., 2018). In addition to the food habits, ethnic differences, and lifestyle of the Kazakh population can greatly contribute to the development of CVD. More than half (53%) of deaths in Kazakhstan are caused by CVD. Kazakhstan is in fourth place with CVD mortality rate among the countries of the Commonwealth of the Independent States. 2 million people suffering from CVD are registered in Kazakhstan, which is 12% of the economically active population of the country. The incidence of stroke in different regions of Kazakhstan is 2.5-3.7 cases per 1000 people per year; the mortality rate is 1.0-1.8 cases per 1000 people per year (Ministry of Healthcare and Social Development, 2016).

In this research we studied the interconnection of metabolic disorders and carotid atherosclerosis in the Kazakh population. Assessment of atherosclerosis and other cardio-metabolic factors in Kazakhstan is an urgent public health problem due to increased mortality from CVD.

## METHODS

### Object of Study

This study included 399 Kazakh patients with atherosclerosis (184 men and 215 women) aged 20-60, who were selected among those who had undergone a medical examination at the Medical Center Hospital of the President's Affairs Administration (Nur-Sultan, Kazakhstan). AS among patients was established by assessing the condition of the carotid artery using color-flow duplex scanning on a cardiovascular ultrasound scanner Vivid E9 by GE Healthcare's (USA). IMC of CCA thickness value (more than 0.9 mm) and the presence of plaques in carotid arteries were taken for arteriogenesis.

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The carotid plaque is a thickening of a focal wall which is at least 0.5 mm or 50% larger than surrounding vascular walls. It is also defined as a focal area with IMC of more than 1.5 mm which protrudes into a lumen different from the adjacent border (Stein et al., 2008).

The study protocol was approved by the Ethics Committee of Medical Center Hospital of the President's Affairs Administration of the Republic of Kazakhstan, and each participant signed informed consent.

We excluded patients with the following features: (1) patients suffering from cancer, infectious diseases, and

those who have serious liver or kidney disease; (2) patients under the age of 20 and older than 60 years old.

As atherosclerosis is associated with high levels of LDL, TG (Nordestgaard, 2016) and BMI (Lovren, Teoh, & Verma, 2015), the participants (399) were divided into two groups according to the levels of each indicator in the blood: LDL (1<sup>st</sup> group <4.0 mmol/L (n=270), 2<sup>nd</sup> group ≥4.0 mmol/L (n=129)); TG (1<sup>st</sup> group <1.7 mmol/L (n=224), 2<sup>nd</sup> group ≥1.7 mmol/L (n=175)); BMI (1<sup>st</sup> group <25 kg/m<sup>2</sup> (n=64), 2<sup>nd</sup> group ≥25 kg/m<sup>2</sup> (n=335)) (Table 1). 2

**Table 1.** Characteristics of groups divided by levels of LDL, BMI and TG

Indicators	Atherosclerosis n=399					
	LDL		BMI		TG	
	1 <sup>st</sup> group <4.0 mmol/L n =270	2 <sup>nd</sup> group ≥4.0 mmol/L n=129	1 <sup>st</sup> group <25 kg/m <sup>2</sup> n=64	2 <sup>nd</sup> group ≥25 kg/m <sup>2</sup> n=335	1 <sup>st</sup> group <1.7 mmol/L n=224	2 <sup>nd</sup> group ≥1.7 mmol/L n=175
Men	117	69	20	165	81	104
Women	153	60	44	170	143	71

A questionnaire was used to collect information about medical history. Patients wore light clothing and no shoes while the weight and height were measured on an automatic anthropometer. Body mass index (BMI) was calculated as weight (kg) divided by height (m) squared.

### Biochemical Blood Test

Blood samples for the study were taken from the ulnar vein in the procedure room after 12 hours of fasting. The plasma of participants in the study was being removed by centrifugation for 10 minutes at 1000×g (4C). For subsequent biochemical analysis, the plasma was maintained at -30C. After centrifugation, serum was used for analysis on the day of blood collection. Levels of glucose, uric acid, TC, TG, HDL, LDL were determined by fermentation method on an automatic clinical chemistry analyzer Architect c8000 (Abbott Laboratories, USA). Atherogenic coefficient (AC) was determined by the formula: AC=(TC-HDL)/HDL.

White blood cells were counted by flow cytometry on an analyzer XN3000 (Sysmex Corporation, Japan).

### Statistical Analysis

Statistical analysis was conducted using SPSS Statistics

software, version 24. The median value of biochemical indicators in groups divided by LDL, BMI, and TG was estimated according to Mann-Whitney U-test. Spearman's rank correlation analysis was used to determine the correlation between lipid parameters and the number of plaques. We conducted binomial logistic regression to determine the impact of obesity, TG level, and age associated with TG, glucose, HDL, arterial hypertension (AH) on plaque occurrence.

### RESULTS

According to Mann-Whitney U-test, in groups divided by LDL (1<sup>st</sup> group <4.0 mmol/L and 2<sup>nd</sup> group ≥4.0 mmol/L), the median value of TG (1.57 against 1.83), AC (2.96 against 3.96) and TC (5.26 against 5.94) were statistically significantly higher in 2<sup>nd</sup> group (p<0.001).

In groups divided by TG (1<sup>st</sup> group <1.7 mmol/L, 2<sup>nd</sup> group ≥1.7 mmol/L) and BMI (1<sup>st</sup> group <25 kg/m<sup>2</sup>, 2<sup>nd</sup> group ≥25 kg/m<sup>2</sup>) median values of the following parameters were statistically significantly higher in 2<sup>nd</sup> group: BMI, white blood cells, HDL, TG, glucose, uric acid, LDL and TC (p<0.05). The median values of TC and LDL were reliably higher in the 2<sup>nd</sup> group divided by TG (p<0.01) (Table 2).

**Table 2.** Median values of biochemical indicators in groups divided by LDL, BMI and TG

Indicators	1 <sup>st</sup> group LDL<4.0 mmol/L, n =270	2 <sup>nd</sup> group LDL≥4.0 mmol/L, n=129	P	1 <sup>st</sup> group BMI<25 kg/m <sup>2</sup> , n=64	2 <sup>nd</sup> group BMI≥25 kg/m <sup>2</sup> , n=335	P	1 <sup>st</sup> group TG<1.7 mmol/L, n=224	2 <sup>nd</sup> group TG>1.7 mmol/L, n=175	P
TC, mmol/L	5.26	5.94	<0.001	5.11	5.51	0.072	5.30	5.94	<0.001
HDL-C, mmol/L	1.19	1.25	0.246	1.39	1.19	<0.001	1.29	1.15	<0.001
LDL-C, mmol/L	3.12	4.33	0.339	3.26	3.39	0.361	3.19	3.54	<0.01
TG, mmol/L	1.57	1.83	<0.001	1.0	1.85	<0.001	1.06	2.56	<0.001
AC	2.96	3.96	<0.001	2.64	3.40	<0.001	2.89	3.94	<0.001
Glucose, mmol/L	5.51	5.63	0.529	5.21	5.69	<0.001	5.44	5.77	<0.001
Uric acid, mmol/L	337.98	334.42	0.078	292.81	345.72	<0.001	321.50	347.31	<0.001
White blood cells, 10 <sup>9</sup> /L	6.68	6.43	0.880	6.03	6.94	<0.001	6.60	6.94	<0.05
BMI kg/m <sup>2</sup>	29.40	30.27	0.936	23.30	30.44	<0.001	28.37	31.18	<0.001

Table 3 shows the prevalence of plaques in women and men. A statistically significant difference was found in the proportion of individuals with 3 or more plaques

between men and women. It can be claimed with a 95% probability that the number of individuals with 3 or more plaques is 4.15% higher among men than women.

**Table 3.** Frequency of plaque occurrence in men and women

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Individuals	men	women	men	women	men	women
<b>Number of plaques</b>	<b>1 plaque n=68</b>		<b>2 plaques n=59</b>		<b>3 and more plaques n=17</b>	
n	29	39	33	26	12	5
p % (CI)	15.68 (10.4-20.9)	18.22 (13.0-23.4)	17.84 (12.3-23.4)	12.15 (7.7-16.50)	6.49 (2.9-10.0)	2.34 (0.3-4.3)
m %	2.67	2.64	2.81	2.23	1.81	1.03
t criterion	-0.68		1.58		1.99	
% difference (CI)	-2.55 (-9.91-4.81)		5.69 (-1.35-12.73)		4.15 (0.06-8.24)	

As a result of conducted Spearman's rank correlation analysis of lipid parameters and the number of plaques, a weak positive correlation was revealed between the number of plaques and AC ( $r=0.22$ ,  $p=0.009$ ) (Figure 1),

IMC of CCA ( $r=0.19$ ,  $p=0.049$ ) (Figure 2). A weak negative correlation between the number of plaques and HDL was revealed as well ( $r=-0.18$ ,  $p=0.031$ ) (Figure 3).

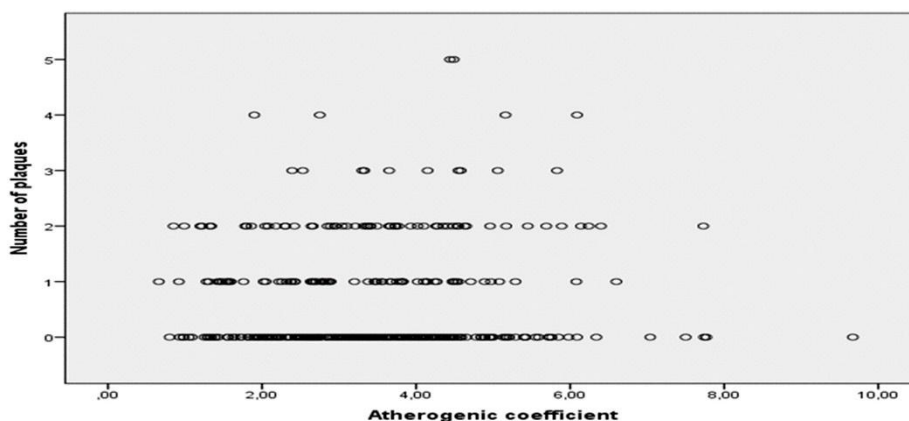


Figure 1. Correlation between the number of plaques and atherogenic coefficient

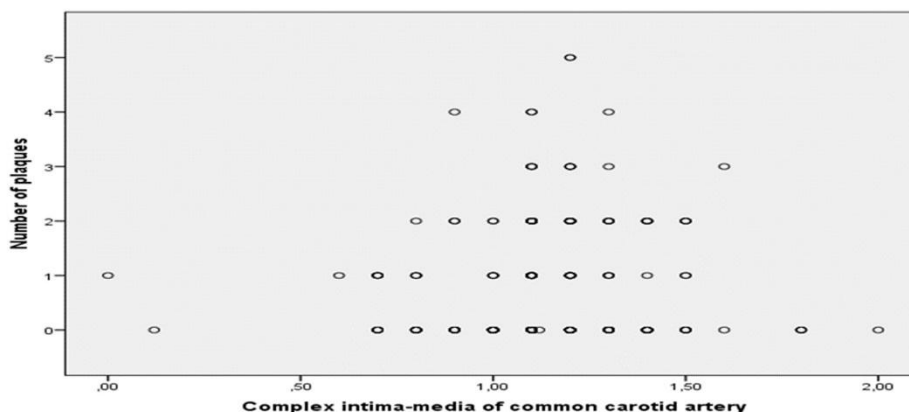


Figure 2. Correlation between the number of plaques and IMC of CCA

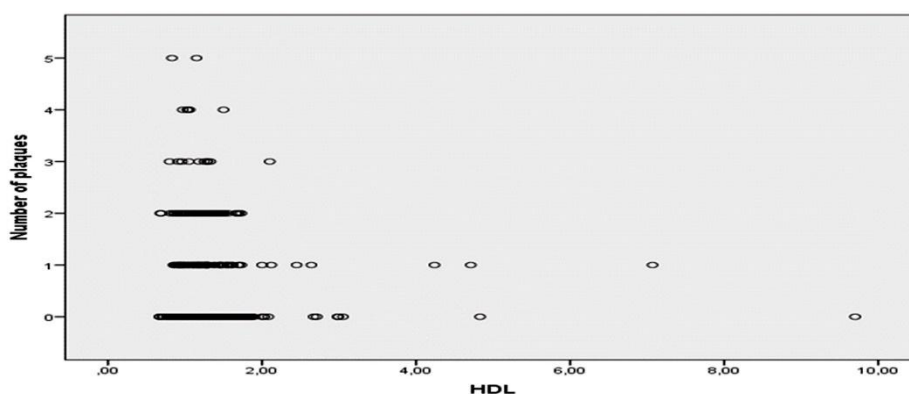


Figure 3. Correlation between the number of plaques and HDL

Binomial logistic regression was conducted in order to determine the impact of obesity, TG level, and age of patients associated with TG, glucose, HDL, AH on the probability of occurrence of plaques (Table 4). The

likelihood of occurrence of plaques increases with the age of the participants in 1.04 times ( $p<0.05$ ). The likelihood of occurrence of plaques increases with the age in 1.35 times ( $p<0.05$ ) with a high level of TG. Moreover, age and

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glucose in 1.25 times ( $p < 0.05$ ), age and low level of HDL in 1.15 times ( $p < 0.05$ ), age and pre-existing AH in 1.27 times ( $p < 0.005$ ), obesity in 1.26 times ( $p < 0.001$ ) and TG

in 1.31 times ( $p < 0.005$ ) increase the probability of occurrence of plaques.

**Table 4.** Binomial logistic regression between indicators and with the occurrence of plaques and increased IMC of CCA

Indicators	Plaque							IMC of CCA		
	Age	Age+TG	Age+glucose	Age+HDL	Age+pre-existing AH	Obesity	TG	Obesity	Age+glucose	Age+HDL
Estimate	0.039	0.041	0.040	-1.915	2.504	0.771	0.266	0.651	0.046	-1.815
Standard Error	0.016	0.016	0.016	0.334	0.857	0.227	0.094	0.209	0.016	0.874
Wald's Chisquare	6.145	6.332	6.223	5.216	8.533	11.941	8.007	9.691	8.387	4.315
p level	<0.05	<0.05	<0.05	<0.05	<0.005	<0.001	<0.005	<0.001	<0.005	<0.05
Standardized Estimate	1.044	1.352	1.125	1.154	1.274	1.263	1.313	1.234	1.125	1.174

Binomial logistic regression was conducted as well to determine the effect of key indicators on the probability of increased IMC of CCA. Obesity in 1.23 times ( $p < 0.001$ ), age with glucose in 1.12 times ( $p < 0.005$ ), age with HDL in 1.17 times increase the risk of IMC of CCA thickening.

### DISCUSSION

Atherosclerosis is a pathologic basis for coronary artery disease, hypertension, and stroke. AS can develop in large and small arteries that supply various organs, including the heart, brain, kidneys, and limbs (Mozaffarian et al., 2016). People with progressive AS have an abnormally increased level of IMC of CCA. Therefore, the identification of serum biomarkers associated with the presence of plaques and with the thickening of IMC of CCA will have a great advantage in the prevention of AS and CVD. Increased levels of circulating LDL-Cholesterol play a key role in AS progression (Schaftenaar, Frodermann, Kuiper, & Lutgens, 2016).

In our study it was found that the risk of AS progression was statistically significantly associated with TG and BMI. In groups with increased TG and  $BMI \geq 25$  kg/m<sup>2</sup> number of white blood cells was significantly higher than in groups  $TG < 1.7$  mmol/L and  $BMI < 25$  kg/m<sup>2</sup>. Some authors found a connection between the number of white blood cells and the risk of atherosclerotic disease development (Yarnell et al., 1991). One study showed that the increased number of white blood cells may be independently connected with a marker for subclinical atherosclerosis (Elkind, Cheng, Boden-Albala, Paik, & Sacco, 2001). Permanent inflammation is a key characteristic of AS and a key factor for leukocyte recruitment for the initiation and progression of lesion development. Therefore, AS may be limited by preventing continuous leukocyte recruitment and stimulating leukocyte migration (Viola & Soehnlein, 2015). Thus, an increased number of white blood cells has been proposed as a new biomarker for predicting future cardiovascular events (Dragu et al., 2008).

In two groups with high levels of BMI and TG indicators of uric acid were significantly higher than in groups with lower similar indicators. A prospective cohort study conducted by Song M with co-authors (Song et al., 2019) showed that uric acid is an independent risk factor of the occurrence of extracranial carotid atherosclerosis in citizens of northern China. Also Jose Carlos Arevalo Lorida with others (Arévalo-Lorido et al., 2019) in their study came to the conclusion that the effect of uric acid on the vessel wall contributes to the development of AS and carotid artery disease. Uric acid contributes to the development of endothelial dysfunction by reducing

nitric oxide bioavailability and enhancing oxidative stress (Bae et al., 2013; Kanbay et al., 2013). It should also be noted that uric acid level may be a sign of the arterial hypertension progression (Benberin, Karabaeva, Vochshenkova, & Sibagatova, 2020).

In both groups with high BMI and TG the lipid profile and BMI indicators were statistically higher. Many studies showed that the lipid profile plays a key role in the pathophysiology of carotid artery thickening (Hou et al., 2018; Yu Wu et al., 2019). The second stage of AS after the carotid artery thickening is the occurrence of plaques. When estimating the correlation between the number of plaques and lipid profile parameters, a weak positive correlation of AC and a weak inverse correlation of HDL with the number of plaques were revealed. One of the reasons for the statistical unreliability of the correlation between the number of plaques with TC and LDL may be a small number of examined people.

The incidence of plaques in our study is 36.09%. A comparative analysis of the presence of plaques (2 and more) in men and women showed that this indicator prevailed in men. These data are similar to the results obtained among Kazakhs living in Xinjiang province of China (Yun Wu et al., 2017).

Our study showed that the risk of plaque occurrence increases with age. Yu R.H. and others (Yu et al., 2009) found a significant correlation between the presence of carotid plaques and age. We also found that age associated with levels of TG, HDL, glucose, pre-existing AH increases the risk of formation of plaque.

Among tested indicators connected with the risk of formation of plaques, we found a significant association of obesity and TG with the occurrence of plaques. Obesity is a prognostic indicator of arterial stiffness and subclinical carotid AS (Hou et al., 2018).

We also found that obesity and association of age with glucose and HDL increases the risk of the thickening of IMC of CCA.

Genetic factors play a major role in the development of AS along with phenotypic indicators (Orekhov et al., 2020; Markin et al., 2020). The next stage of our work will be a molecular genetic study of the development of AS in the Kazakh population.

### CONCLUSIONS

Thus, with hypertriglyceridemia and overweight inflammatory processes and metabolic disorders proceed markedly. Dyslipidemia/hyperlipidemia leads to an increased number of plaques in carotid arteries. The number of plaques equal to 3 or more is more common in men. Obesity and lipid profile parameters are specific

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prognostic markers for carotid atherosclerosis in the Kazakh population. For a deep understanding of the role of metabolic indicators in the risk of AS, it is necessary to carry out a study with a wider selection of participants and conduct molecular genetic studies.

## Conflict of Interest Statement

None of the authors have anything to disclose.

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