Melnikov I.S.[1, 2], Kozlov S.G.[1], Pogorelova O.A.[1], Tripoten M.I.[1], Saburova O.S.[1], Khamchieva L.S.[1], Avtaeva Yu. N.[1], Zvereva M. D.[1], Prokofjeva L. V.[1], Kuznetsova T. V.[1], Guseva O. A.[1], Balakhonova T. V.[1, 3], Gabbasov Z. A.[1]

[1] Chazov National Medical Research Centre of Cardiology, Moscow, Russia

[2] State Research Center of the Russian Federation, Institute for Biomedical Problems, Moscow, Russia

[3] Sechenov First Moscow State Medical University, Moscow, Russia

Monomeric form of C-reactive protein in the assessment of the residual inflammatory cardiovascular risk in patients with subclinical carotid atherosclerosis

Aim	To study the relationship between monomeric C-reactive protein (mCRP) and the progression of asymptomatic carotid atherosclerosis in patients with a moderate risk for cardiovascular diseases (CVD) as assessed with the SCORE model.
Material and methods	The study included 80 men and women aged 53.1±5.8 years assigned to the category of a moderate risk for CVDs by the SCORE model with a low-density lipoprotein cholesterol (LDL-C) level of 2.7–4.8 mmol/l and asymptomatic, hemodynamically insignificant (<50% luminal narrowing) carotid atherosclerosis according to ultrasonic data. All patients were prescribed atorvastatin to achieve a LDL-C level <2.6 mmol/l. After 7 years of follow-up, ultrasonic examination of carotid arteries was performed, and concentrations of high-sensitivity C-reactive protein (hsCRP) and mCRP were measured.
Results	A concentration of LDL-C <2.6 mmol/l was achieved in all patients. The progression of atherosclerosis as determined by an increased number of atherosclerotic plaques (ASPs), was observed in 45 (56%) patients. At 7 months of follow-up, concentrations of cCRP were higher in the group of patients with progressive carotid atherosclerosis, while the levels of hsCRP did not differ between the groups. Increased mCRP concentrations were associated with changes in variables of the "atherosclerotic load", including the number of ASPs, total ASP height, and the intima-media thickness (IMT). In patients with a median mCRP concentration of 5.2 [3.3; 7.1] μg/l and more, the increases in mean ACP number and total ASP height were considerably higher than in patients with mCRP concentrations lower than the median (3.9 and 2.7 times, respectively), whereas the odds ratio for the progression of asymptomatic carotid atherosclerosis was 5.5 (95% confidence interval, CI: 2.1–14.6; p=0.001). ROC analysis showed that the concentration of hsCRP had no predictive value for prognosis of asymptomatic carotid atherosclerosis (p=0.16), while the area under the ROC curve (AUC) for mCRP was 0.75±0.056 (95% CI: 0.64–0.86; p=0.001).
Conclusion	According to the results of 7-year follow-up, the plasma concentration of mCRP was significantly higher in patients with an increased number of ASPs than in patients without this increase. An increased level of mCRP may indicate a higher inflammatory risk of CVD.

Keywords	Monomeric C-reactive protein; mCRP; hsCRP; residual inflammatory risk; carotid atherosclerosis
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Corresponding author	Gabbasov Z. A. E-mail: zufargabbasov@yandex.ru

Decreasing low-density lipoprotein (LDL) cholesterol is a critical element of the main strategies used to prevent the development and progression of atherosclerosis. In several large randomized clinical trials, LDL cholesterol was significantly reduced during the intense lipid-lowering therapy, even brought to extremely low values in some patient groups. However, the incidence of cardiovascular complications decreased less than expected [1]. The risk of cardiovascular diseases and subsequent complications that persists despite vigorous lipid-lowering therapy and the elimination of other modifiable risk factors is identified as the residual cardiovascular risk [2, 3]. The residual

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"inflammatory" risk associated with long-term subclinical inflammation in atherosclerotic plaques is one of the main types of the residual cardiovascular risk [2, 3].

Residual inflammatory risk is determined by the blood levels of C-reactive protein (CRP) using a highly sensitive test (hs-CRP) – ≥2.0 mg/L [2]. CRP levels recorded when measuring hs-CRP represents the plasma concentration of pentameric CRP (pCRP), which is produced in the liver during the stimulation by pro-inflammatory cytokines, primarily interleukin-6 [2]. At the areas of local inflammation, pCRP interacts with oxidized lipoproteins, which are dissociated a monomeric state (mRSB), as well as damaged cell membranes and their microparticles [4]. Following dissociation, mCRP continues to be mainly associated with cell membranes and is found, among other things, in atherosclerotic plaques [5], where it is predominantly localized in the lipid nucleus, around newly formed microvessels, and in areas where macrophages, T-cells, and smooth muscle cells accumulate [6]. mCRP with its pro-inflammatory properties stimulate the production of pro-inflammatory cytokines IL-8 and IL-6, polarization of macrophages and T-cells into an inflammatory phenotype, and stimulation of neoangiogenesis [7].

Studying mCRP as a biomarker of inflammation may provide new diagnostic and prognostic information. No clinical trials have been conducted to determine the levels of mCRP as a biomarker of inflammation that predicts the cardiovascular risk.

Objective

Study the correlation between the plasma levels of monomeric C-reactive protein and the progression of asymptomatic carotid atherosclerosis in patients at a moderate cardiovascular risk according to the SCORE scale.

Material and Methods

The study included 80 male and female patients at the age of 40–65 years who have a moderate risk of developing CVDs according to the SCORE scale, LDL cholesterol levels of 2.7–4.8 mmol/L, and asymptomatic hemodynamically insignificant (<50% of the vessel lumen narrowing) carotid atherosclerosis shown by ultrasound examination.

The study did not include patients with coronary artery disease (CAD), a history of transient ischemic attacks and acute cerebrovascular accidents, symptomatic atherosclerosis of peripheral arteries, atherosclerosis of the carotid and peripheral arteries with lumen narrowing of ≥ 50 %, aortic aneurysm, diabetes mellitus type 1 and type 2, familial hypercholesterolemia, arterial hypertension, chronic kidney disease (MDRD glomerular filtration rate < 60 mL/min/1.73 m^2 and/or serum creatinine > 150 μmol/L), LDL cholesterol ≥ 4.9 mmol/L and ≤ 2.6 mmol/L, triglycerides > 4.5 mmol/L, increased activity of alanine aminotransferase and/or aspartate aminotransferase 3-fold or more of the upper limit of normal, a cardiovascular risk of ≥ 5 % (SCORE), chronic inflammatory diseases, including of autoimmune origin, malignancies, allergic sensitization of the body, those who received lipid-lowering therapy in the past 12 months, and had contraindications to statins.

The cumulative cardiovascular risk was estimated by the SCORE scale, lipid metabolism was analyzed, and carotid ultrasound examination was performed in patients meeting the inclusion criteria. Atorvastatin was administered to the included patients at individual doses to achieve target LDL cholesterol levels of <2.6 mmol/L. Patients were followed up by cardiologists for seven years with annual visits and monitoring of lipid metabolism. At the end of the follow-up period, all patients were subjected to repeat ultrasound examination of the carotid arteries, determination of the blood lipid composition and plasma levels of hs-CRP and mCRP. There was no hemodynamically significant carotid stenosis at the end of follow-up, which is why the progression of atherosclerosis was established by an increased number of atherosclerotic plaques [8]. Patients were divided into the groups with progressing and non-progressing carotid atherosclerosis. Patients were divided into groups by mCRP levels: below the median and level equal to or above the median.

Carotid ultrasound examination was performed using a iU-22 ultrasound machine through a linear sensor with an operating frequency range of 3–9 MHz using B-mode, color flow mapping in the power and rapid-series modes. All examinations were performed by a single operator. The number of atherosclerotic plaques was quantified all over the length of the common carotid artery (CCA), internal carotid artery (ICA), and the CCA bifurcation on both sides (a total of six arterial segments). A carotid atherosclerotic plaque represented a local mass protruding into the artery lumen by at least 0.5 mm or by an amount equal to 50 % of the surrounding intima-media thickness (IMT), or a local mass with IMT > 1.5 mm [9]. The total number of all plaques and their cumulative height in the six segments of interest were calculated. IMT was measured on the posterior wall of the distal segments of both CCAs at 1 cm proximal to the bifurcation. IMT was defined as the distance between the intima-lumen boundary and the media-adventitia boundary. Three anterior and lateral measurements were made on each side. IMT of the right and left CCAs was calculated based on the of six means of three consecutive measurements via anterior access and three consecutive measurements by lateral access. Averaged IMT was calculated as the half sum of the IMTs of the right and left CCAs.

Blood was collected from the ulnar vein in the morning after 12 hour fasting into a tube containing 3.8 % sodium citrate in the ratio of 1 part of anticoagulant to 9 parts of blood. Platelet-poor plasma was obtained by blood centrifuging

at 2000 g for 20 min at room temperature. Plasma levels of mCRP were measured by the original method [10] using functional polystyrene microspheres BD Cytometric Bead Array conjugated with monoclonal anti-mCRP antibodies produced in clone 8C8. FITC-conjugated polyclonal anti-CRP antibodies of clone GAHCRP were used as developing antibodies. Tests were performed is a BD FACSCanto II flow cytofluorimeter, and information was collected and processed using the FACSDiva software program.

The variability of mCRP was estimated using the original method in the first 20 patients included in the study, 12 months before the completion of the seven-year follow-up and at the end of the follow-up. The mean mCRP level was 7.06±8.22 μg/L 12 months before the end of the seven-year follow-up and 7.21 ± 8.99 μg/L at the end of the seven-year follow-up (Δ +2 %; p = 0.73).

Tests to determine the levels of hs-CRP and parameters of blood lipid metabolism were performed in the clinical biochemistry laboratory of the Academician Chazov National Medical Research Center.

Normally distributed values obtained during the study are expressed as the means ± standard deviations, non-normally distributed values are presented as the medians (upper and lower quartiles). Statistical hypotheses of the types of distribution were tested using the Shapiro-Wilk W-test. Comparative analysis of the data of the two independent groups was performed using the Mann-Whitney U-test and the data of the dependent groups were compared using the Wilcoxon test. The differences were statistically significant with p value less than 0.05. All tests were two-tailed. Statistical analysis was performed using Statistica v. 6.0 and SPSS Statistics v. 17.0.

The study was approved by the ethics committee of the Academician Chazov National Medical Research Center. The study was conducted following the Declaration of Helsinki. All patients signed written informed consent.

Results

Baseline clinical characteristics of patients are detailed in Table 1.

All patients received atorvastatin to achieve target LDL cholesterol levels of <2.6 mmol/L. Patients were treated with atorvastatin at the mean dose of 25±10.0 mg/day in the progressing atherosclerosis group and 26±11 mg/day in the non-progressing atherosclerosis (p=0.7). After the seven-year follow-up period, patients with progressing atherosclerosis had mean TC of 4.07±0.42 mmol/L, LDL cholesterol of 2.2±0.33 mmol/L, triglycerides 1.36±0.58 mmol/L, and HDL cholesterol 1.31±0.36 mmol/L. Patients with non-progressing atherosclerosis had TC 3.92±0.54 mmol/L, LDL cholesterol of 2.06±0.35 mmol/L, triglycerides 1.35±0.74 mmol/L, and HDL cholesterol 1.22±0.31 mmol/L. LDL cholesterol levels measured after seven years of follow-up differed statistically significantly between the groups (p=0.037). There were no differences between the groups in other indicators of lipid metabolism. Moreover, after seven years of follow-up, no differences were identified in sex, smoking status, burdened family history, body mass index (BMI), and obesity between the groups of patients with progressing and non-progressing asymptomatic carotid atherosclerosis.

During the seven-year follow-up, cardiovascular complications occurred in 5 patients with progressing carotid atherosclerosis, including myocardial infarction (n=2), exertional angina (n=2), and ischemic stroke (n=1). Cardiovascular complications occurred in 2 patients with non-progressing carotid atherosclerosis (exertional angina). In the group of patients with progressing carotid atherosclerosis, 6 patients developed diabetes mellitus type 2 and 22 patients had arterial hypertension. In the group of patients with non-progressing carotid atherosclerosis, 1 patient developed diabetes mellitus type 2 and 16 patients developed arterial hypertension.

At the end of the seven-year follow-up, the progression of subclinical carotid atherosclerosis was observed in 45 (56 %) patients (30 male and 15 female). Changes in the ultrasound carotid artery parameters in patients with progressing and non-progressing carotid atherosclerosis are presented in Table 2.

In the group of patients with progressing carotid atherosclerosis, mean hs-CRP was 2.23 ± 2.63 mg/L, which did not differ significantly from patients with non-progressing carotid atherosclerosis with 1.46 ± 1.27 mg/L (p=0.23). In the group of patients with non-progressing carotid atherosclerosis, mean hs-CRP was 8.8 ± 7.54 mg/L, which was higher than in patients with non-progressing carotid atherosclerosis with mCRP of 5.96 ± 8.35 mg/L (p = 0.0006).

Median mCRP was 5.2 [3.3; 7.1] μg/L. The group with mCRP < 5.2 μg/L included 39 patients (22 male and 17 female), and the group with mCRP ≥5.2 μg/L included 41 patients (25 male and 16 female). Atherosclerosis progressed in 14 (36 %) patients in the group with mCRP < 5.2 μg/L and in 31 (76%) patients with mCRP ≥ 5.2 μg/L. Changes in ultrasound parameters depending on the mCRP levels according to the results of the seven-year follow-up is presented in Table 3.

In the group of patients with mCRP above the median, an increase in the mean number of atherosclerotic plaques per patient was 41 % higher and an increase in the cumulative height of atherosclerotic plaques was 32% higher than in the group of mCRP below the median (Figure 1).

The odds ratio of the progression of asymptomatic carotid atherosclerosis in patients with mCRP ≥5.2 μg/L was 5.5 (95% confidence interval (CI) 2.1–14.6; p=0.001). The ROC curve analysis was conducted to describe the prognostic value of hs-CRP and mCRP in predicting the progression of asymptomatic

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Table 1. Clinical characteristics of patients at the time of inclusion

Parameter	Patients with progressing asymptomatic carotid atherosclerosis (n=45)	Patients with non-progressing asymptomatic carotid atherosclerosis (n=35)	p
Age, years	53 ± 6	53 ± 6	0.72
Male/female	30 (67%)/15 (33%)	17 (49%)/18 (51%)	0.12
Burdened family history	9 (20%)	8 (23%)	0.76
Smoking	12 (27%)	10 (29%)	0.51
BMI, kg/m^2	27.9 ± 5.3	26.9 ± 4.0	0.68
Patients with BMI ≥ 30 kg/m^2	13 (29%)	7 (20%)	0.37
TC, mmol/L	5.74 ± 0.74	5.6 ± 0.91	0.72
LDL cholesterol, mmol/L	3.67 ± 0.62	3.74 ± 0.74	0.42
HDL cholesterol, mmol/L	1.18 ± 0.33	1.19 ± 0.28	0.93
TG, mmol/L	1.75 ± 0.96	1.58 ± 0.84	0.46

BMI, body mass index; TC, total cholesterol; LDL, low density lipoproteins; HDL, high-density lipoproteins; TG, triglycerides.

Table 2. Changes in ultrasound parameters of carotid arteries based on the results of 7-year follow-up

Parameter	Patients with progressing carotid atherosclerosis (n = 45)			Patients with non-progressing carotid atherosclerosis (n = 35)		
	baseline	7 years	Δ, %	baseline	7 years	Δ, %
Mean number of plaques per patient	2.07 ± 1.14	3.56 ± 1.37	+72*	2.71 ± 1.41	2.6 ± 1.44	-4^{NS}
Sum of plaque heights, mm	5.11 ± 4.17	8.54 ± 4.78	+67*	6.3 ± 4.4	6.35 ± 4.38	+1^{NS}
IMT of the right CCA, mm	0.73 ± 0.14	0.79 ± 0.14	+8*	0.66 ± 0.11	0.69 ± 0.14	+5*
IMT of the left CCA, mm	0.71 ± 0.14	0.77 ± 0.15	+8*	0.67 ± 0.13	0.72 ± 0.16	+7^{NS}
Averaged IMT, mm	0.72 ± 0.13	0.78 ± 0.13	+8*	0.67 ± 0.11	0.71 ± 0.13	+6*

IMT, intima media thickness; CCA, common carotid artery;
* p<0.05; ^{NS}, statistically insignificant.

Table 3. Changes in ultrasound parameters depending on the mCRP levels according to the results of 7-year follow-up

Parameter	mCRP < 5.2 μg/L (n = 39)			mCRP ≥ 5.2 μg/L (n = 41)		
	baseline	7 years	Δ, %	baseline	7 years	Δ, %
Number of plaques per patient	2.54 ± 1.35	2.9 ± 1.41	+14*	2.17 ± 1.22	3.37 ± 1.51	+55*
Sum of plaque heights, mm	5.85 ± 3.75	6.95 ± 4.15	+19*	5.42 ± 4.78	8.18 ± 5.17	+51*
IMT of the right CCA, mm	0.67 ± 0.12	0.72 ± 0.15	+7*	0.72 ± 0.14	0.77 ± 0.14	+7*
IMT of the left CCA, mm	0.67 ± 0.12	0.74 ± 0.15	+10*	0.71 ± 0.15	0.75 ± 0.17	+6^{NS}
Averaged IMT, mm	0.67 ± 0.11	0.73 ± 0.14	+9*	0.72 ± 0.13	0.76 ± 0.14	+6*

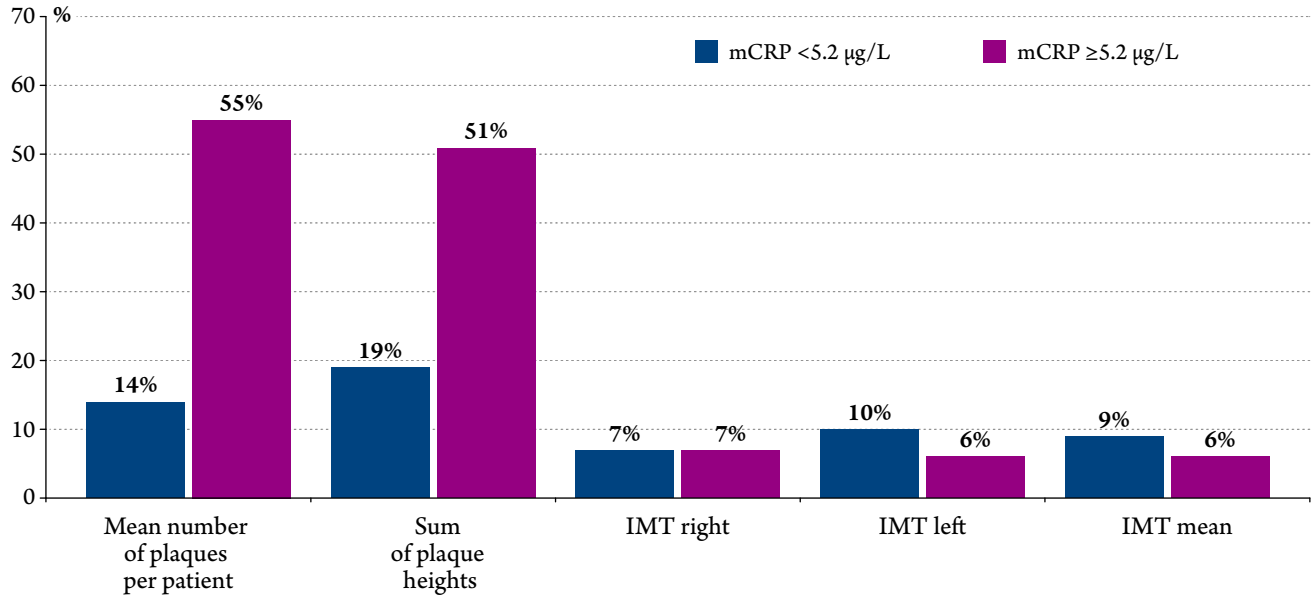
mCRP, monomeric C-reactive protein; IMT, intima-media thickness; CCA, common carotid artery;
* p<0.05; ^{NS}, statistically insignificant.

carotid atherosclerosis. The area under the curve (AUC) was 0.75 ± 0.056 (95 % CI 0.64–0.86; p = 0.001) for mCRP and 0.59 ± 0.064 (95 % CI 0.47–0.72; p = 0.16) for hs-CRP. The best-possible combination of sensitivity (0.69) and specificity (0.71) was achieved at the cutoff threshold of mCRP 5.1 μg/L (Figure 2).

Discussion

Clinical guidelines for the prevention of atherosclerosis consider the detection of asymptomatic atherosclerosis in patients with low and moderate cardiovascular risk, as determined by the SCORE scale, during the ultrasound examination of carotid arteries as a ground for reclassifying the risk category and administering lipid-lowering statin therapy in order to prevent or significantly delay the development of the first cardiovascular complications [11]. The risk group was reclassified to high risk following the Russian guidelines for CVD prevention in effect at the time of inclusion in 2012–2013 [12], in which the target level for LDL cholesterol was < 2.6 mmol/L. All included patients

Figure 1. Changes in ultrasound parameters of carotid arteries in patients with mCRP levels less or more than the median (5.2 μg/L) based to the results of 7-year follow-up



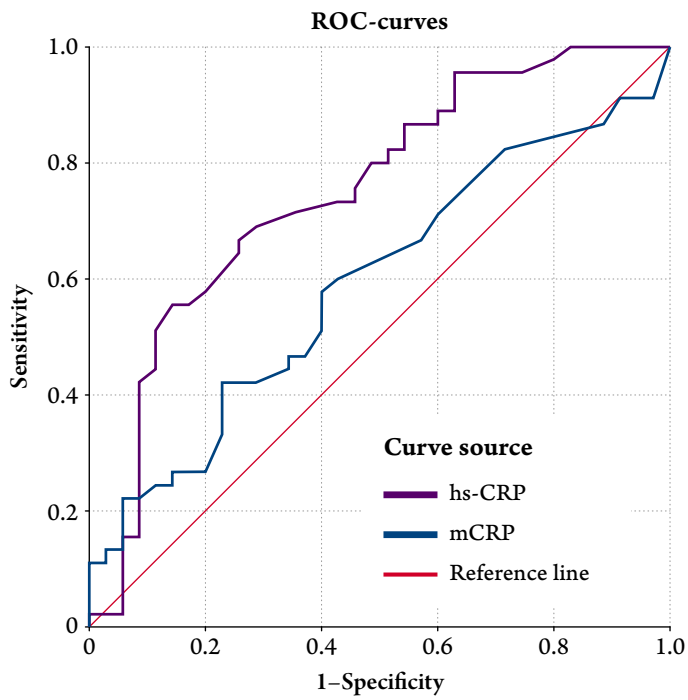
mCRP, monomeric C-reactive protein; CCA, common carotid artery; IMT, intima media thickness; significant change from the baseline ($p<0.05$).

receiving atorvastatin achieved target LDL cholesterol levels. However, the progression of carotid atherosclerosis was observed in 45 (56 %) patients at the end of the seven-year follow-up.

Groups differed statistically significantly in terms of mCRP and did not differ in hs-CRP. The odds ratio of the progression of asymptomatic carotid atherosclerosis in patients with mCRP ≥ 5.2 μg/L was 5.5 (95 % CI 2.1–14.6; p=0.001). The ROC curve analysis showed that hs-CRP had no predictive value in predicting the progression of asymptomatic carotid atherosclerosis (p = 0.16), and the area under the curve (AUC) for mCRP was 0.75 ± 0.056 (95 % CI 0.64–0.86; p = 0.001).

The levels of mCRP have not been previously assessed in patients with asymptomatic carotid atherosclerosis. There are three known studies, in which serum or plasma levels of mCRP were measured. Wang et al. [13] described the measurement of plasma mCRP in patients with acute myocardial infarction, unstable and stable angina. The highest levels of mCRP were found in patients with acute myocardial infarction (20.96±1.64 μg/L), especially in patients who died within the first 30 days (36.70 ± 10.26 μg/L), and mCRP was not detected in blood plasma in patients with stable angina or healthy individuals [13]. Zhang et al. [14] determined the mean plasma levels of mCRP in patients with eczema, psoriasis, urticaria, and in healthy individuals from 15.2 μg/L to 59.8 μg/L. Williams et al. [15] calculated mean serum levels of mCRP 1000.03±110.0 μg/L and hs-CRP of more than 100 mg/L in patients with acute inflammation. Plasma levels of mCRP in our patients were lower than in the described

Figure 2. ROC curves describing the prognostic value of hs-CRP and mCRP in predicting the progression of asymptomatic carotid atherosclerosis



studies (8.8±7.54 μg/L and 5.96±8.35 μg/L in patients with progressing and non-progressing asymptomatic carotid atherosclerosis, respectively). This may be due to the fact that the included patients had few traditional cardiovascular risk factors for, no co-morbidities, and they received statins.

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Elevated hs-CRP is associated with an unfavorable cardiovascular prognosis [2]. However, given the main risk factors, hs-CRP was not an independent predictor of the progression of asymptomatic carotid atherosclerosis in a 13 year prospective study Tromsø, which included 6,503 patients [16]. A three-year study, which included 3,122 patients, also showed that hs-CRP was not an independent predictor of increased IMT when considering the main risk factors [17].

Conclusion

The plasma levels of monomeric C-reactive protein in patients with increasing numbers of atherosclerotic plaques after seven years of follow-up was statistically significantly higher than in patients without an increase. The study findings suggest that increased levels of monomeric C-reactive protein may indicate an increased inflammatory risk of developing cardiovascular diseases.

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REFERENCES

1. Dimmitt SB, Stampfer HG, Martin JH, Warren JB. Clinical benefits of evolocumab appear less than hoped. The Lancet. 2018;391(10124):933–4. DOI: 10.1016/S0140-6736(18)30530-0
2. Ridker PM. Anticytokine Agents: Targeting Interleukin Signaling Pathways for the Treatment of Atherothrombosis. Circulation Research. 2019;124(3):437–50. DOI: 10.1161/CIRCRESAHA.118.313129
3. Bershtein LL. New Possibilities to Reduce the Residual Risk in Patients with Ischemic Heart Disease. Kardiologiia. 2020;60(11):110–6. [Russian: Берштейн Л.Л. Новые возможности снижения резидуального риска при ишемической болезни сердца. Кардиология. 2020;60(11):110-6]. DOI: 10.18087/cardio.2020.11.n1370
4. Braig D, Nero TL, Koch H-G, Kaiser B, Wang X, Thiele JR et al. Transitional changes in the CRP structure lead to the exposure of proinflammatory binding sites. Nature Communications. 2017;8(1):14188. DOI: 10.1038/ncomms14188
5. Eisenhardt SU, Habersberger J, Murphy A, Chen Y-C, Woollard KJ, Bassler N et al. Dissociation of Pentameric to Monomeric C-Reactive Protein on Activated Platelets Localizes Inflammation to Atherosclerotic Plaques. Circulation Research. 2009;105(2):128–37. DOI: 10.1161/CIRCRESAHA.108.190611
6. Krupinski J, Turu MM, Martinez-Gonzalez J, Carvajal A, Juan-Babot JO, Iborra E et al. Endogenous Expression of C-Reactive Protein Is Increased in Active (Ulcerated Noncomplicated) Human Carotid Artery Plaques. Stroke. 2006;37(5):1200–4. DOI: 10.1161/01.STR.0000217386.37107.be
7. McFadyen JD, Kiefer J, Braig D, Loseff-Silver J, Potempa LA, Eisenhardt SU et al. Dissociation of C-Reactive Protein Localizes and Amplifies Inflammation: Evidence for a Direct Biological Role of C-Reactive Protein and Its Conformational Changes. Frontiers in Immunology. 2018;9:1351. DOI: 10.3389/fimmu.2018.01351
8. Hashimoto H, Kitagawa K, Hougaku H, Shimizu Y, Sakaguchi M, Nagai Y et al. C-Reactive Protein Is an Independent Predictor

of the Rate of Increase in Early Carotid Atherosclerosis. Circulation. 2001;104(1):63–7. DOI: 10.1161/hc2601.091705
9. Touboul P-J, Hennerici MG, Meairs S, Adams H, Amarenco P, Bornstein N et al. Mannheim Carotid Intima-Media Thickness and Plaque Consensus (2004 - 2006 - 2011). An update on behalf of the advisory board of the 3rd, 4th and 5th watching the risk symposia, at the 13th, 15th and 20th European Stroke Conferences, Mannheim, Germany, 2004, Brussels, Belgium, 2006, and Hamburg, Germany, 2011. Cerebrovascular Diseases. 2012;34(4):290–6. DOI: 10.1159/000343145
10. Zvereva M.D., Saburova O.S., Melnikov I.S., Kozlov S.G., Gabbasov Z.A. Monomeric C-reactive protein in coronary artery disease. Complex Issues of Cardiovascular Diseases. 2020;9(2):45–52. [Russian: Зверева М.Д., Сабурова О.С., Мельников И.С., Козлов С.Г., Габбасов З.А. Современные возможности определения и применения в клинике мономера С-реактивного белка. Комплексные проблемы сердечно-сосудистых заболеваний. 2020;9(2):45-52]. DOI: 10.17802/2306-1278-2020-9-2-45-52
11. Ershova A.I., Balakhonova T.V., Ivanova A.A., Meshkov A.N., Boytsov S.A., Drapkina O.M. The problem of cardiovascular risk stratification depending on the severity of carotid and femoral artery atherosclerosis. Cardiovascular Therapy and Prevention. 2020;19(2):75–81. [Russian: Ершова А.И., Балахонова Т.В., Иванова А.А., Мешков А.Н., Бойцов С.А., Драпкина О.М. Проблема стратификации сердечно-сосудистого риска в зависимости от выраженности атеросклероза сонных и бедренных артерий. Кардиоваскулярная терапия и профилактика. 2020;19(2):75-81]. DOI: 10.15829/1728-8800-2020-2441
12. Aronov D.M., Arabidze G.G., Akhmedzhanov N.M., Balakhonova T.V., Boytsov S.A., Bubnova M.G. et al. Diagnostics and correction of lipid metabolism disorders in order to prevent and treat atherosclerosis. Russian guidelines (V revision). Atherosclerosis. 2012;8(2):61–94. [Russian: Аронов Д.М., Арабидзе Г.Г., Ахмеджанов Н.М., Балахонова Т.В., Бойцов С.А., Бубнова М.Г. и др. Диагностика и Коррекция Нарушений Липидного Обмена с Целью Профилактики и Лечения Атеросклероза. Российские Рекомендации (V пересмотр). Атеросклероз. 2012;8(2):61-94]
13. Wang J, Tang B, Liu X, Wu X, Wang H, Xu D et al. Increased monomeric CRP levels in acute myocardial infarction: A possible new and specific biomarker for diagnosis and severity assessment of disease. Atherosclerosis. 2015;239(2):343–9. DOI: 10.1016/j.atherosclerosis.2015.01.024
14. Zhang L, Li H-Y, Li W, Shen Z-Y, Wang Y-D, Ji S-R et al. An ELISA Assay for Quantifying Monomeric C-Reactive Protein in Plasma. Frontiers in Immunology. 2018;9:511. DOI: 10.3389/fimmu.2018.00511
15. Williams RD, Moran JA, Fryer AA, Littlejohn JR, Williams HM, Greenhough TJ et al. Monomeric C-Reactive Protein in Serum With Markedly Elevated CRP Levels Shares Common Calcium-Dependent Ligand Binding Properties With an in vitro Dissociated Form of C-Reactive Protein. Frontiers in Immunology. 2020;11:115. DOI: 10.3389/fimmu.2020.00115
16. Eltoft A, Arntzen KA, Hansen J-B, Wilsgaard T, Mathiesen EB, Johnsen SH. C-reactive protein in atherosclerosis – A risk marker but not a causal factor? A 13-year population-based longitudinal study: The Tromsø study. Atherosclerosis. 2017;263:293–300. DOI: 10.1016/j.atherosclerosis.2017.07.001
17. Lorenz MW, Karbstein P, Markus HS, Sitzer M. High-Sensitivity C-Reactive Protein Is Not Associated With Carotid Intima-Media Progression: The Carotid Atherosclerosis Progression Study. Stroke. 2007;38(6):1774–9. DOI: 10.1161/STROKEAHA.106.476135

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