

# Stenotic atherosclerotic lesions of carotid arteries in type 2 diabetes: the most significant risk factors

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Significant prevalence of atherosclerosis and its complications in patients with type 2 diabetes (T2D) determines need in further investigations of existing risk factors (RF).

**Study object:** to identify the most significant RF for the carotid stenotic lesions development in T2D patients.

**Materials and methods.** The correlation analysis between surrogate atherosclerosis markers (carotid intima-media thickness (IMT), atherosclerotic plaques (AP), degree of the carotid stenosis) and mean systolic blood pressure (SBP), body mass index (BMI), anxiety index (from Hospital anxiety and depression rating scale (HADRS)); mean serum level of lipids, HbA1c, high sensitivity C-reactive protein (hsCRP), uric acid (UA) during 5 years observation in 145 patients with T2D (mean age – 53,0 (49,0–60,5) years) was done. Statistical analysis was performed using IBM SPSS Statistics 20.

**Results.** Direct medium-strength correlations between IMT and mean SBP ( $r=0,38$ ), mean levels of hsCRP ( $r=0,41$ ), UA ( $r=0,40$ ), HbA1c ( $r=0,44$ ), total cholesterol (TC) ( $r=0,40$ ), low-density lipoprotein cholesterol (LDL-C) ( $r=0,41$ ), anxiety index ( $r=0,40$ ) were found. At the same time the degree of carotid stenosis was also directly correlated with mean levels of hsCRP ( $r=0,41$ ), HbA1c ( $r=0,42$ ), TC ( $r=0,37$ ), LDL-C ( $r=0,32$ ). The incidence of carotid AP was increased in 3 fold in patients with mean hsCRP > 3,0 mg/L ( $\chi^2(1)=29,9$ ,  $\phi=0,454$ ; RR:3,62; 95% CI:1,91–6,84), 2 fold – in patients with mean HbA1c > 8,5% ( $\chi^2(1)=7,9$ ,  $\phi=0,259$ ; RR:2,50; 95% CI:1,13–2,98) and TC > 4,5 mmol/L ( $\chi^2(1)=9,3$ ,  $\phi=0,253$ ; RR:2,51; 95% CI:1,15–5,46); in 1,5 fold – in patients with mean LDL-C > 2,6 mmol/L ( $\chi^2(1)=4,3$ ,  $\phi=0,272$ ; RR:1,67; 95% CI:1,0–2,99).

**Conclusion.** The most significant RF for the stenotic carotid atherosclerotic lesions development in patients with T2D are hsCRP > 3,0 mg/L, HbA1c > 8,5%, TC > 4,5 mmol/L, LDL-C > 2,6 mmol/L, UA > 300  $\mu\text{mol/L}$ , SBP > 140 mmHg, HADRS score > 11 units and BMI > 25 kg/m<sup>2</sup>.

**Key words:** type 2 diabetes, cardiovascular risk factors, atherosclerosis, intima-media thickness, atherosclerotic plaques.

The most common cause of complications and disability in patients with type 2 diabetes (T2D) is cardiovascular disease (CVD), which is observed in more than half of the patients, and in 65% of cases is the leading cause of death [1].

The basis for CVD development is atherosclerotic vascular lesions. Atherosclerosis is a common chronic disease of the body with an undulating course, which is based on metabolic disorders, chronic inflammatory reaction, accompanied with thickening of wall of arteries as a result of chronic degenerative lesion and specific intimal proliferation leading to development of atherosclerotic plaques (AP).

Atherosclerosis is a multifactorial disease. Etiology and pathogenesis of atherosclerosis is still not exactly clear, but negative effects on the vascular wall of the low-density cholesterol (LDL-C) and high blood pressure are proven. It's also well known that constant stress promotes the progression of athero-

sclerosis by violation of the neuro-endocrine regulation of lipid metabolism [2].

Several studies, including the MONICA study, have shown that classical risk factors (RF) of atherosclerosis can not fully explain the development of cardiovascular complications. This led to the searching for other causes of atherothrombosis and new RF, which promote development and the rate of progression of complications of CVD [3].

To these new RF of CVD, presented at the annual congress of the European Society of Cardiology and the American College of Cardiology, levels of high sensitivity C-reactive protein (hsCRP) and uric acid (UA) in serum were attributed [4].

The intima-media thickness (IMT) of common carotid artery (CA) is a surrogate marker of the systemic atherosclerosis and associated with coronary artery disease and coronary heart disease. For example, when analyzing the results of eight studies involving 37,197 patients, it was shown that the increase of IMT in 0,1 mm is associated with increased risk of myocardial infarction from 10% to 15% [5].

One of the main problems of the atherosclerosis diagnosis is that atherosclerosis is not evident until essentially violation of blood circulation has happened in an organ which artery is impressed by atherosclerosis and the degree of stenosis of the affected artery is more than 50% [6].

According to Spence JD et al. research, atherosclerotic plaque (AP) area increases in 2,4 times faster than growing IMT. Therefore, detection of AP presence in carotid arteries is associated with higher cardiovascular risk compared than thickening of intima-media [7].

Consequently, the understanding of correlation between atherosclerosis and RF and correct interpretation of their combination from the first moment of contact between doctor and patient, will allow to choose the most optimal diagnostic and therapeutic interventions in patients management. These findings are especially important for patients with T2D, who are in high risk of cardiovascular complications development.

**Study object:** to identify the most significant risk factors for the carotid stenotic lesions development in type 2 diabetes patients.

## MATERIALS AND METHODS

The study was conducted at the Family Medicine Department of the Shupyk National Medical Academy of Postgraduate Education based on Public nonprofit enterprise "Center of the primary care «Rusanivka», endocrinology department of the «Kyiv Regional Clinical Hospital» and Public nonprofit enterprise «Center of primary care № 3» Shevchenko district (Kyiv), during 2011–2015.

145 patients with T2D (mean age – 53,0 (49,0–60,5) years; 72 men (49,7%) and 73 women (50,3%) were enrolled in the study.

The patients with a glomerular filtration rate less than 60 ml/min, autoimmune diseases, acute inflammatory diseases and other serious conditions and diseases were excluded from the study.

The pair correlation analysis results

Indicator	SBP, mmHg	BMI, kg/m <sup>2</sup>	Score of HADRS, units	hsCRP, mg/L	UA $\mu$ mol/L	HbA1c, %	Total cholesterol, mmol/L	LDL-C, mmol/L	IMT, mm	Stenosis, %
SBP, mmHg	1	0,28	0,15	0,21	0,11	0,19	0,16	0,19	0,38**	0,16
BMI, kg/m <sup>2</sup>	0,28	1	0,16	0,31**	0,26	0,15	0,22	0,25	0,29	0,09
Score of HADRS, units	0,15	0,16	1	0,36**	0,25	0,26	0,25	0,28	0,40**	0,16
hsCRP, mg/L	0,21	0,31**	0,36**	1	0,37**	0,38**	0,27	0,28	0,41**	0,41**
UA, $\mu$ mol/L	0,11	0,26	0,25	0,37**	1	0,12	0,29	0,27	0,40**	0,19
HbA1c, %	0,19	0,15	0,26	0,38**	0,12	1	0,25	0,27	0,44**	0,42**
Total cholesterol, mmol/L	0,16	0,22	0,25	0,27	0,29	0,25	1	0,91**	0,40**	0,37*
Low-density lipoproteins cholesterol (LDL-C), mmol/L	0,19	0,25	0,28	0,28	0,27	0,27	0,91**	1	0,41**	0,32*
IMT, mm	0,38**	0,29	0,40**	0,41**	0,40**	0,44**	0,40**	0,41**	1	0,60**
Stenosis, %	0,16	0,09	0,16	0,41**	0,19	0,42**	0,37*	0,32*	0,60**	1

\*\* – significant correlation  $p < 0,01$ .

Table 2

Predictors of IMT thickening (&gt;0,9 mm) and AP development in carotid arteries of T2D patients

Indicator	IMT more than 0.9 mm				Atherosclerotic plaque (stenosis more than 20%)			
	RR	95% CI	$\chi^2(1)$	$\phi$	RR	95% CI	$\chi^2(1)$	$\phi$
SBP > 140 mmHg	1,73	1,29-2,32	14,7	0,319	-	-	-	-
BMI > 25 kg/m <sup>2</sup>	2,41	1,0-5,0	8,1	0,235	-	-	-	-
hsCRP > 3,0 mg/L	2,07	1,32-3,23	15,6	0,328	3,62	1,91-6,84	29,9	0,454
UA > 300 $\mu$ mol/L	2,08	1,46-2,97	22,1	0,390	-	-	-	-
HbA1c > 8,5%	1,72	1,02-2,72	5,8	0,363	2,50	1,13-2,98	7,9	0,259
Total cholesterol > 4,5 mmol/L	1,63	1,0-2,86	4,3	0,272	2,51	1,15-5,46	9,3	0,253
LDL-C > 2,6 mmol/L	-	-	2,6	-	1,67	1,0-2,99	4,3	0,272
More than 11 units by HADRS	2,15	1,49-3,10	13,5	0,303	-	-	-	-

Note: RR – relative risk, CI – confidence interval,  $\chi^2$  – criterion of correlation,  $\phi$  – criterion of strength of correlation.

All patients received proper medical treatment according to the existing protocols for T2D patients management (Order of the Ministry of Health of Ukraine from 21.12.2012 №1118 «Approval and introduction of the medical and technological documents for standardization of medical care in type 2 diabetes»).

For all enrolled in the study patients comprehensive clinical (measurement of systolic blood pressure (SBP), estimation of body mass index (BMI), evaluation of the emotional state of patients by Hospital anxiety and depression rating scale (HADRS), laboratory (serum levels of the lipids, HbA1c, hsCRP and uric acid (UA) and sonographic (duplex color scanning of carotids with IMT measurement, AP and vessels stenosis determination) examination was done at the beginning of the study and during observation period.

Statistical analysis was performed using IBM SPSS Statistics 20.

## RESULTS

The results of the correlation analysis between CVD RF and surrogate markers of atherosclerosis in patients with T2D is presented in Table 1.

As shown in the Table 1, a direct medium-strength correlation between carotid IMT and mean SBP ( $r=0,38$ ,  $p<0,01$ ), hsCRP ( $r=0,41$ ,  $p<0,01$ ), UA ( $r=0,40$ ,  $p<0,01$ ), HbA1c ( $r=0,44$ ,  $p<0,01$ ), TC ( $r=0,40$ ,  $p<0,01$ ), LDL-C ( $r=0,41$ ,  $p<0,01$ ) and average score of HADRS ( $r=0,40$ ,  $p<0,01$ ) for the observed period was found.

Furthermore, a direct medium-strength correlation between carotid stenosis and mean serum levels of hsCRP ( $r=0,41$ ,  $p<0,01$ ), HbA1c ( $r=0,42$ ,  $p<0,01$ ), TC and LDL-C for the period of observation was found. At the same time the correlation between carotid stenosis and lipids was a bit more weak (for TC ( $r=0,37$ ,  $p<0,05$ ) and for LDL-C ( $r=0,32$ ,  $p<0,05$ ) which can point at the more significant influence of the inflammatory process on the stenosis development.

The significance of the different CVD RF for IMT thickening > 0,9 mm and AP development T2D patients was evaluated of the relative risk (RR) and criterion of strength of correlation ( $\phi$ ). Results are presented in Table 2.

As shown in Table 2, the incidence of IMT thickening over 0,9 mm increases in more than 1,5 fold in patients with mean SBP above 140 mmHg ( $\chi^2(1) = 14,7$ ,  $\phi = 0,319$ ; RR: 1,73; 95% CI: 1,29–2,32), HbA1c > 8,5% ( $\chi^2(1) = 5,8$ ,  $\phi = 0,363$ ; RR: 1,72; 95% CI: 1,02–2,72), TC > 4,5 mmol/L ( $\chi^2(1) = 4,3$ ,  $\phi = 0,272$ ; RR: 1,63; 95% CI: 1,0–2,86); in 2 fold – in patients with hsCRP > 3,0 mg/L ( $\chi^2(1) = 15,6$ ,  $\phi = 0,328$ ; RR: 2,07; 95% CI: 1,32–3,23), UA > 300  $\mu$ mol/L ( $\chi^2(1) = 22,1$ ,  $\phi = 0,390$ ; RR: 2,08; 95% CI: 1,46–2,97) and BMI > 25 kg/m<sup>2</sup> ( $\chi^2(1) = 8,1$ ,  $\phi = 0,235$ ; RR: 2,41; 95% CI: 1,0–5,0). The long term anxiety state (more than 11 units by HADRS) doubled the incidence of IMT > 0,9 mm ( $\chi^2(1) = 13,5$ ,  $\phi = 0,303$ ; RR: 2,15; 95% CI: 1,49–3,10).

The incidence of AP detection increased in more than 3 fold

in patients with mean hsCRP > 3,0 mg/L ( $\chi^2(1)=29,9$ ,  $\phi=0,454$ ; RR:3,62; 95% CI:1,91–6,84); in 2 fold with mean HbA1c > 8,5% ( $\chi^2(1)=7,9$ ,  $\phi=0,259$ ; RR:2,50; 95% CI:1,13–2,98) and TC > 4,5 mmol/L ( $\chi^2(1)=9,3$ ,  $\phi=0,253$ ; RR:2,51; 95% CI:1,15–5,46); 1,5 fold – when LDL-C > 2,6 mmol/L ( $\chi^2(1)=4,3$ ,  $\phi=0,272$ ; RR:1,67; 95% CI:1,0–2,99) during observation period ( $p<0,05$ ).

**Стенозирующее атеросклеротическое поражение каротид у больных сахарным диабетом 2-го типа: наиболее значимые факторы риска**  
**Л.В. Химмон, М.А. Рыбicka**

Значительная распространенность атеросклероза и его осложнений у больных сахарным диабетом (СД) 2-го типа определяет необходимость в дальнейших исследованиях существующих факторов риска (ФР).

**Цель исследования:** определить наиболее значимые ФР развития стенозирующего атеросклеротического поражения сонных артерий (СА) у больных СД 2-го типа.

**Материалы и методы.** Проводился корреляционный анализ между суррогатными маркерами атеросклероза (толщина комплекса интима–медиа (ТКИМ), наличие атеросклеротических бляшек (АБ), процент стеноза СА) и средними показателями систолического артериального давления (САД), индекса массы тела (ИМТ), эмоционального состояния пациентов по шкале тревоги и депрессии (HADRS), липидограммы, HbA1c, высокочувствительного С-реактивного белка (вЧСРБ), мочевой кислоты (МК) в сыворотке крови в динамике в течение 5 лет у 145 больных СД 2-го типа (средний возраст – 53,0 (49,0–60,5) года). Статистический анализ проведен с помощью IBM SPSS Statistics 20.

**Результаты.** Обнаружена прямая связь средней силы между ТКИМ и средними показателями САД ( $r=0,38$ ), вЧСРБ ( $r=0,41$ ), МК ( $r=0,40$ ), HbA1c ( $r=0,44$ ), общего холестерина (ОХС) ( $r=0,40$ ), ХС ЛПНП ( $r=0,41$ ), количеством баллов по HADRS ( $r=0,40$ ). Процент стеноза просвета СА имел прямую связь средней силы со средними уровнями вЧСРБ ( $r=0,41$ ), HbA1c ( $r=0,42$ ), ОХС ( $r=0,37$ ), ХС ЛПНП ( $r=0,32$ ). Частота выявления АБ в просвете СА увеличивалась в 3 раза при средних показателях за период наблюдения вЧСРБ>3,0 мг/л ( $\chi^2(1)=29,9$ ,  $\phi=0,454$ ; ОР=3,62 (ДИ:1,91–6,84), в 2 раза при HbA1c>8,5% ( $\chi^2(1)=7,9$ ,  $\phi=0,259$ ; ОР=2,50 (ДИ:1,13–2,98) и ОХС>4,5 ммоль/л ( $\chi^2(1)=9,3$ ,  $\phi=0,253$ ; ОР=2,51 (ДИ:1,15–5,46)), в 1,5 раза – у пациентов с ХС ЛПНП>2,6 ммоль/л ( $\chi^2(1)=4,3$ ,  $\phi=0,272$ ; ОР=1,67 (ДИ:1,0–2,99)).

**Выводы.** Наиболее значимые ФР развития стенозирующего атеросклеротического поражения каротид: вЧСРБ>3,0 мг/л, HbA1c>8,5%, ОХС>4,5 ммоль/л, ХС ЛПНП>2,6 ммоль/л, МК>300 мкмоль/л, САТ>140 мм рт.ст., более 11 баллов по шкале HADRS и ИМТ>25 кг/м<sup>2</sup>.  
**Ключевые слова:** сахарный диабет 2-го типа, факторы сердечно-сосудистого риска, атеросклероз, толщина комплекса интима–медиа, атеросклеротические бляшки.

**CONCLUSION**

The most significant predictors of the carotid stenotic atherosclerotic lesions development in T2D patients are hsCRP > 3,0 mg/L, HbA1c > 8,5%, TC > 4,5 mmol/L, LDL-C > 2,6 mmol/L, UA > 300 μmol/L, SBP > 140 mmHg, HADRS > 11 units and BMI > 25 kg/m<sup>2</sup>.

**Стенозующее атеросклеротичне ураження каротид у хворих на цукровий діабет 2-го типу: найбільш значущі фактори ризику**  
**Л.В. Хімiон, М.О. Рибicka**

Значна поширеність атеросклерозу та його ускладнень у хворих на цукровий діабет (ЦД) 2-го типу визначає необхідність в подальших дослідженнях існуючих факторів ризику (ФР).

**Мета дослідження:** визначити найбільш значущі ФР розвитку стенозувального атеросклеротичного ураження сонних артерій (СА) у хворих на ЦД 2-го типу.

**Матеріали та методи.** Проводився кореляційний аналіз між суррогатними маркерами атеросклерозу (товщина комплексу інтима–медіа (ТКИМ), наявність атеросклеротичних бляшок (АБ), відсоток стенозу СА) та середніми показниками систолического артеріального тиску (САТ), індексу маси тіла (ІМТ), емоційного стану пацієнтів за шкалою тривоги і депресії (HADRS), ліпідограми, HbA1c, високочутливого С-реактивного білка (вЧСРБ), сечової кислоти (СК) у сироватці крові в динаміці протягом 5 років у 145 хворих на ЦД 2-го типу (середній вік – 53,0 (49,0–60,5) року). Статистичний аналіз проведений за допомогою IBM SPSS Statistics 20.

**Результати.** Виявлений прямий зв'язок середньої сили між ТКИМ і середніми показниками САТ ( $r=0,38$ ), вЧСРБ ( $r=0,41$ ), СК ( $r=0,40$ ), HbA1c ( $r=0,44$ ), загального холестерину (ЗХС) ( $r=0,40$ ), ХС ЛПНП ( $r=0,41$ ), кількістю балів за HADRS ( $r=0,40$ ). Відсоток стенозу просвіту СА мав прямий зв'язок середньої сили з середніми рівнями вЧСРБ ( $r=0,41$ ), HbA1c ( $r=0,42$ ), ЗХС ( $r=0,37$ ), ХС ЛПНП ( $r=0,32$ ). Частота виявлення АБ в просвіті СА збільшувалася в 3 рази при середніх показниках за період спостереження вЧСРБ>3,0 мг/л ( $\chi^2(1)=29,9$ ,  $\phi=0,454$ ; ВР=3,62 (ДІ:1,91–6,84), в 2 рази при HbA1c>8,5% ( $\chi^2(1)=7,9$ ,  $\phi=0,259$ ; ВР=2,50 (ДІ:1,13–2,98) та ЗХС>4,5 ммоль/л ( $\chi^2(1)=9,3$ ,  $\phi=0,253$ ; ВР=2,51 (ДІ:1,15–5,46)), в 1,5 разу – у пацієнтів з ХС ЛПНП>2,6 ммоль/л ( $\chi^2(1)=4,3$ ,  $\phi=0,272$ ; ВР=1,67 (ДІ:1,0–2,99)).

**Висновок.** Найбільш значущі ФР розвитку стенозувального атеросклеротичного ураження каротид: вЧСРБ>3,0 мг/л, HbA1c>8,5%, ЗХС>4,5 ммоль/л, ХС ЛПНП>2,6 ммоль/л, СК>300 мкмоль/л, САТ>140 мм рт.ст., більше 11 балів за шкалою HADRS та ІМТ>25 кг/м<sup>2</sup>.

**Ключові слова:** цукровий діабет 2-го типу, фактори серцево-судинного ризику, атеросклероз, товщина комплексу інтима–медіа, атеросклеротичні бляшки.

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Статья поступила в редакцию 16.02.2016