Original article

Role of dyslipidemia, chronic kidney disease and hypertension on carotid atherosclerosis in elderly patients with type 2 diabetes mellitus

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Abstract

Aging triggers thickening of the intima and stiffening of the arterial walls especially in the presence of known risk factors of atherosclerosis such as hypertension, dyslipidemia, and chronic kidney disease (CKD).

We investigated the possible role of dyslipidemia, hypertension and CKD on the characteristics of carotid atherosclerosis (presence of plaque, carotid IMT and TPA) in elderly patients with DT2. We investigated 76 patients with DT2 who presented consecutively to this institute. Control group included 24 healthy subjects the same age. Patients aged 60–75 years with DT2 were included in this study. The mean age of the subjects was 65.54 ± 4.37 years (from 60 to 75 years). 45.6% (n = 31) of them were men and 54.4% (n = 37) were women. Plasma total cholesterol, high-density lipoprotein cholesterol, and triglyceride concentrations were measured. Estimated glomerular filtration rate (eGFR) was

Address: Volha Vasilkova 246025 Gomel 8 Inogorodnyay 2-10-23 E-mail: vmanka@mail.ru defined and calculated using the CKD-EPI (chronic kidney disease epidemiology collaboration) equation. High-resolution B-mode ultrasonography was performed with a duplex scanner (VIVID 9 EXP) equipped with a 4.5–12 MHz linear array transducer. The intima-media thickness (IMT) was measured using automated edge detection software.

Results. We divided all patients (DT2 and control) into 3 groups: Group 1 (n = 24) – patients did not have any additional atherosclerosis risk factor, Group 2 (n = 25) – patients had one additional atherosclerosis risk factor, and Group 3 (n = 43) – patients had two or three additional atherosclerosis risk factors. Using multiple linear regression analysis adjusted for confounding factors, IMT and TPA were significantly correlated with age > 60 years (β = 0.359, p < 0.0001; β = 0.263, p < 0.0001), hypertension (β = 0.041, p = 0.003; β = 0.126, p < 0.0001), dyslipidemia (β = 0.066, p = 0.0001; β = 0.125, p < 0.0001) and CKD (β = 0.054, p = 0.003; β = 0.165, p < 0.0001), respectively. We found a significant difference in carotid IMT between left and right carotid artery (0.70 ± 0.16 mm versus 0.66 ± 0.13 mm, p < 0.001, respectively). There were significant difference in

carotid IMT between left and right carotid artery $(0.70 \pm 0.16 \text{ mm} \text{ versus } 0.66 \pm 0.13 \text{ mm}, \text{ p} < 0.001, \text{ respectively}).$

Conclusion. In elderly patients with DT2 the presence of dyslipidemia, hypertension, and different CKD status were predictors of carotid plaque. Thus, early diagnosis and treatments of hypertension, dyslipidemia, and CKD are necessary for diabetic patients to prevent and reduce cardiovascular and cerebrovascular morbidity and mortality in aged patients with diabetes.

Key words:

dyslipidemia, chronic kidney disease, hypertension, carotid atherosclerosis, type 2 diabetes mellitus

Introduction

Type 2 diabetes mellitus (DT2), which is an endocrine and metabolic disease, has become the third most common type of non-infectious disease worldwide following cardiovascular disease and cancer [1]. DT2 is often associated with several other cardiovascular risk factors that have an important role to play in the beginning and the evolution of atherosclerosis over its long natural history from endothelial function to clinical events [2]. Atherosclerotic complications are the leading causes of morbidity and mortality among patients with DT2 [3].

It has been suggested that patients with DT2 have thicker and stiffer carotid arteries and are more likely to suffer from cerebrovascular events[4, 5]. Aging also triggers thickening of the intima and stiffening of the arterial walls especially in the presence of known risk factors of atherosclerosis such as hypertension, dyslipidemia, and chronic kidney disease (CKD) [6, 7]. Moreover, these proatherosclerotic diseases are common complications in patients with DT2 [8, 9]. However, it is still unclear whether the clustering of these risk factors cumulatively increases the carotid atherosclerosis burden in elderly patients with DT2.

Previously studies have shown that mean carotid intima-media thickness (IMT) is a valid marker of early carotid atherosclerosis assessed from pathology [10, 11] and is associated with risk factors for atherosclerotic disease [12]. Carotid IMT and plaque assessment by cervical ultrasonography is a noninvasive, feasible, and accurate method for detecting asymptomatic carotid atherosclerosis [13]. It is also largely used for risk assessment in primary prevention and in clinical trials as a surrogate endpoint for cardiovascular and cerebral events. Both IMT and total plaque area (TPA) are associated with an increased risk of ischemic stroke and coronary heart disease [14]. It is well established that the presence of carotid plaques represents advanced carotid atherosclerosis, often symptomatic, whereas IMT can be assessed in the absence of focal plaques and symptoms [15].

Thus, in this study, we investigated the possible role of dyslipidemia, hypertension and CKD on the characteristics of carotid atherosclerosis (presence of plaque, carotid IMT and TPA) in elderly patients with DT2.

Subjects and methods

Subjects

Ethical approval was obtained from the special committee of The Republican Research Centre for Radiation Medicine and Human Ecology (Gomel, Republic of Belarus). We investigated 76 patients with DT2 who presented consecutively to this institute. Control group included 24 healthy subjects the same age.

Patients aged 60–75 years with DT2 were included in this study. Criteria for the diagnosis of DT2 included symptoms of diabetes (excessive urination, constant thirst, tiredness, blurred vision) and a fasting plasma glucose indicative of impaired fasting glucose (6.1 mmol/L) and a casual plasma glucose concentration 11.1 mmol/L. Casual was defined as any time of day without regard to time of the last meal.

Patients with previous radiotherapy of the neck, carotid endarterectomy, and carotid stenting were excluded. Written informed consent was obtained from all patients. All patients were treated with diet, oral antidiabetic drugs (biguanides and sulfonylureas), and/or insulin.

Other atherosclerosis risk factors of subjects, including smoking, hypertension, dyslipidemia, and CKD, were identified with a questionnaire and a blood test. However, there was only 8 smokers in the 76 recruited patients with DT2 and was subsequently excluded to avoid statistical bias. As a result, a total of 68 elderly patients with DT2 were included in the study. The mean age of the subjects was 65.54 ± 4.37 years (from 60 to 75 years). 45.6% (n = 31) of them were men and 54.4% (n = 37) were women.

Assessment of atherosclerosis risk factors

For each patient, blood pressure will be recorded in the sitting position in both arms to the nearest 2 mmHg using a mercury sphygmomanometer. Two readings will be taken 5 min apart, and the mean of two will be taken as the blood pressure.

Plasma total cholesterol, high-density lipoprotein cholesterol, and triglyceride concentrations were measured using standard enzymatic methods. Low-density lipoprotein cholesterol was calculated using the Friedewald et al. equation [16]. Hemoglobin A1c (HbA1c) was measured using high-performance liquid chromatography.

The levels of blood glucose and creatinine were determined by automated clinical chemistry analyzer using reagent cartridges recommended by the manufacturer (Dimension Xpand Plus, Siemens Healthcare, Germany).

Estimated glomerular filtration rate (eGFR) was defined and calculated using the CKD-EPI (chronic kidney disease epidemiology collaboration) equation [17]. Patients were interviewed and their medical history of coronary heart disease, stroke, smoking, and medical treatments of hypertension, dyslipidemia, and CKD was obtained. The presence of smoking, hypertension, dyslipidemia, and CKD was identified with the following criteria [18, 19]: smoking: current smoker consuming 10 cigarettes per day for at least six months; hypertension: blood pressure \geq 140/90 mmHg or under hypotensive medication; dyslipidemia: fasting total cholesterol \geq 4.5 mmol/L, low density lipoprotein \geq 2.6 mmol/L, high density lipoprotein \leq 1.0 mmol/L (for men) and \leq 1.3 mmol/L (for women), triglyceride ≥ 1.7 mmol/L or under medication to lower level of cholesterol; CKD: eGFR < 60 mL/min per 1.73 m² or with kidney damage.

Carotid Ultrasound Measurements

High-resolution B-mode ultrasonography was performed with a duplex scanner (VIVID 9 EXP) equipped with a 4.5–12 MHz linear array transducer.

The intima-media thickness (IMT) was measured using automated edge detection software as the distance between the lumen-intima interface and the media-adventitia interface. All examinations were performed by a single experienced examiner, who was blind to the clinical and biochemical data.

Atherosclerotic plaque was defined as a focal structure encroaching into the arterial lumen of 0.5 mm or 50% of the surrounding IMT value or IMT of > 1.5 mm. Total plaque area (TPA) was calculated as the sum of all plaque areas.

Statistical Analyses

Characteristics of the study population are presented as mean (SD) \pm standard deviation (SD), or numbers (percentages). Paired *t*-test and Wilcoxon signed ranks test were used to compare the measurements at the left and right carotid arteries of the same individuals. Multivariate linear regression analysis was performed to evaluate the association between IMT and TPA and other parameters adjusted for age, sex, dyslipidemia, CKD and hypertension. A p-value < 0.05 was considered statistically significant. All statistical analyses were performed using SPSS v11.0 software (SPSS Japan, Tokyo, Japan).

Results

The characteristics of study participant are shown in Table 1. In the 68 patients with DT2, the mean blood glucose and HbA1c level were 8.52 ± 3.10 mmol/L and $6.59 \pm 1.88\%$, respectively. We divided all patients (DT2 and control) into 3 groups: Group 1 (n = 24) – patients did not have any additional atherosclerosis risk factor, Group 2 (n = 25) – patients had one additional atherosclerosis risk factor, and Group 3 (n = 43) – patients had two or three additional atherosclerosis risk factors. There were significant differences of blood glucose and HbA1c level between Group 1 and Group 2, 3 (Table 1; p < 0.05).

Using multiple linear regression analysis adjusted for confounding factors, IMT and TPA were significantly correlated with age >60 years (β = 0.359, p<0.0001; β = 0.263, p<0.0001), hypertension (β = 0.041, p = 0.003; β = 0.126, p<0.0001), dyslipidemia (β = 0.066, p = 0.0001; β = 0.125, p<0.0001) and CKD (β = 0.054, p = 0.003; β = 0.165, p<0.0001), respectively. However, gender (men) was not significantly correlated with IMT (p = 0.171) and TPA (p = 0.112) (Table 2).

The results of the study suggested that the left carotid artery in patients with DT2 was more vulnerable to atherosclerosis when compared with the right carotid artery. So, we found a significant difference in carotid IMT between left and right carotid artery $(0.70 \pm 0.16 \text{ mm versus} 0.66 \pm 0.13 \text{ mm, p} < 0.001$, respectively). There were no significant difference in carotid IMT between patients with plague and without plague (p = 0.171).

Discussion

The prevalence of DT2 is rising dramatically in industrialized countries [20]. Well known, that diabetes mellitus is a common cause of atherosclerosis [21], and
 Table 1. Demographic and ultrasonographic characteristics in patients with DT2 and control with different numbers of atherosclerosis risk factors

	Groups with different number of atherosclerosis risk factor					
Parameters	Group 1 (0) n=24	Group 2 (1) n=25	Group 3 (≥2) n=43	р		
Age, years	65.13 ± 3.48	65.54 ± 4.37	66.38 ± 4.53	-		
Gender (female/male), n	11/13	14/16	17/21	-		
Presence of plaque, n	2	8	20	0.016*		
Hypertension, n	-	10	37	-		
Dyslipidemia, n	-	8	17	-		
CKD, n	-	0	5	-		
Coronary heart disease, n	0	6	29	-		
Stroke, n	0	1	3	-		
Blood glucose, mmol/l	$4.65 \pm 2.12*$	8.83 ± 4.27	8.28 ± 2.09	0.01		
Hemoglobin A1c, %	$4.38 \pm 1.15*$	6.49 ± 1.85	6.78 ± 2.13	0.04		
Total cholesterol, mmol/L	5.01 ± 1.11	5.05 ± 1.09	5.24 ± 1.44	0.08		
Triglyceride, mmol/L	1.53 ± 0.78	1.54 ± 0.81	1.89 ± 1.10	0.203		
High-density lipoprotein cholesterol, mmol/L	2.84 ± 0.89	2.95 ± 0.95	3.25 ± 1.00	0.124		
Low-density lipoprotein cholesterol, mmol/L	1.24 ± 0.31	1.37 ± 0.36	1.16 ± 0.32	0.814		
eGFR, mL/min per 1.73 m ²	$97.15 \pm 24.12*$	84.68 ± 36.60	79.40 ± 23.74	0.02		
IMT, mm	0.73 ± 0.02	0.78 ± 0.01	0.81 ± 0.02	0.441		
TPA, mm ²	11.31 ± 0.12	12.36 ± 0.23	13.18 ± 0.15	0.213		

CKD: Chronic kidney disease; IMT: intima-media thickness;

TPA: total area plaque; eGFR: estimated glomerular filtration rate;

* p value indicates significant difference.

Table 2. Multivariate linear regression analysis for putative predictors of IMT and TPA in elderly DT2 patients

Parameters	IMT			TPA		
	β†	r ²	р	β†	r ²	р
Gender (men)	0.177	0.039	0.171	0.136	0.020	0.112
Age > 60 years	0.359	0.145	< 0.0001	0.263	0.099	< 0.0001
Hypertension	0.041	0.001	0.003	0.126	0.014	< 0.0001
Dyslipidemia	0.066	0.004	0.0001	0.125	0.019	< 0.0001
CKD	0.054	0.003	0.002	0.165	0.026	< 0.0001

All variants are adjusted for the analysis.

b: standardized regression coefficient; CKD: Chronic kidney disease;

IMT: intima-media thickness; TPA: total area plaque.

Table 3. Carotid IMT of right and left carotid artery in DT2 patients

	DT2 patients					
Parameter	The patients with plaque n = 40	The patients without plaque n = 28	р	The left carotid artery n = 68	The right carotid artery n = 68	р
IMT, mm	0.71 ± 0.11	0.67 ± 0.13	0.171	0.70 ± 0.16	0.66 ± 0.13	< 0.001

* p value indicates significant difference; IMT: intima-media thickness.

patients with diabetes tend to suffer hypertension, dyslipidemia, and CKD, which are also classical risk factors of atherosclerosis [22]. These risk factors are also associated with preclinical atherosclerosis, generally measured as the intima-media thickness of carotid arteries [23, 24, 25]. It is correlated with all traditional vascular risk factors and regarded as an 'intermediate phenotype' of atherosclerosis or a marker of subclinical organ damage. Carotid IMT independently predicts cardiovascular events [26].

In this study, we showed that DT2 patients with more additional atherosclerosis risk factors had higher incidence of carotid plaque (8% versus 32%/42%, respectively, p<0.05). In addition, in elderly patients with DT2, gender did not have significant effects on IMT and TPA, whereas the age > 60 years old and the presence of hypertension,

dyslipidemia, and CKD were independent predictors of carotid atherosclerosis ($r^2 = 0.145$, p < 0.0001; $r^2 = 0.001$, p = 0.003; $r^2 = 0.004$, p = 0.0001; $r^2 = 0.003$; p = 0.002, respectively).

However, despite the difference between the number of atherosclerotic plaques and the number of proatherosclerotic factors carotid IMT did not significantly increase in these groups. This result is consistent with a previous study in which diabetes and hypertension did not have additive effect on carotid thickening and stiffening [27]. It might be due to the fact that the common carotid artery was used for the measurement of carotid IMT. The Mannheim consensus recommends that IMT should be measured in segments without plaque[28]; thus, the most advanced atherosclerotic lesions will not be included in the IMT measurements. Atherosclerotic plaques occur predominantly at sites of no laminar turbulent flow in the carotid artery typically in the bifurcation and the proximal internal segment. Because high-precision IMT measurements are more easily obtained in segments in the far wall of the distal part of the common carotid artery, many researchers prefer to measure IMT in this arterial segment, but this approach will not capture atherosclerotic manifestations downstream in the artery [29].

Hypertension, dyslipidemia, and CKD induce abnormal shearing pressure to the endothelium, greater circulating cholesterol level, and more severe oxidative stress in blood, respectively [30]. The common carotid artery may be less influenced by these proatherosclerotic conditions, while the bifurcation and bulb may be more susceptible to these factors and be easier to have atherosclerotic changes. Thus measurements in the common carotid artery may not fully reflect atherosclerotic burdens in the carotid artery. This conclusion was also supported by other findings of the present study that there were no significant differences of carotid IMT between patients with and without carotid plaque (0.71 ± 0.11 mm versus 0.67 ± 0.13 mm, p = 0.171, respectively).

In our study we found that the left carotid artery in elderly patients with DT2 was more vulnerable to atherosclerosis in comparison with the right carotid artery. There were significant difference in carotid IMT between left and right carotid artery (0.70 ± 0.16 mm versus 0.66 ± 0.13 mm, p < 0.001, respectively). This result was consistent with Luo's study in which the left carotid arterial wall was thicker than the right in the elderly as well as in the subjects with atherosclerotic diseases[31]. This fact can be explained by the anatomy of the circulation

system. The left carotid artery is closer to the heart and arises directly from the aorta, whereas the right carotid artery arises from the brachiocephalic trunk [32]. It turns out that the left carotid artery is longer than 20 - 25 mm. The different origins of the left and right carotid arteries induce different haemodynamics to the two arteries. If there are proatherosclerotic conditions, the asymmetric haemodynamics of the left and right carotid arteries may induce the development of carotid atherosclerosis at different degrees [33, 34].

Several limitations need to be addressed in the present study. First, our sample size was relatively small and thus the additive effects of atherosclerosis risk factors on carotid atherosclerosis in elderly patients with DT2 may be not fully evaluated. Because of limited number of subjects with smoking, this study did not assess the additive effect of smoking on carotid atherosclerosis in DT2. Although previously studies have shown that smoking is an important predictor of atherosclerosis in DT2 patients [35]. Further studies with larger sample size are needed to clarify the contribution of additional atherosclerosis risk factors to atherosclerosis of carotid artery in elderly patients with DT2.

Conclusion

We showed the role of additional atherosclerosis risk factors to carotid atherosclerosis in elderly patients with DT2. In these patients, the presence of dyslipidemia, hypertension, and different CKD status were predictors of carotid plaque. Thus, early diagnosis and treatments of hypertension, dyslipidemia, and CKD are necessary for diabetic patients to prevent adverse cardiovascular and cerebrovascular outcomes and reduce cardiovascular and cerebrovascular morbidity and mortality in aged patients with diabetes.

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DISLIPIDEMIJOS, LĖTINĖS INKSTŲ LIGOS IR ARTERINĖS HIPERTENZIJOS REIKŠMĖ SENYVO AMŽIAUS PACIENTŲ, SERGANČIŲ 2 TIPO CUKRINIU DIABETU, MIEGO ARTERIJŲ ATEROSKLEROZĖS IŠSIVYSTYMUI

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Santrauka

Senėjimas greitina kraujagyslių intimos sustorėjimą ir arterijų sienelių standumą, ypač esant rizikos veiksniams, tokiems kaip arterinė hipertenzija, dislipidemija ir lėtinė inkstų liga (LIL).

Tyrimo tikslas – ištirti dislipidemijos, arterinės hipertenzijos ir LIL įtaką miego arterijų ateroskleroziniams požymiams (plokštelės nustatymas, miego arterijų IMS ir TPA) senyviems pacientams, sergantiems 2 tipo cukriniu diabetu. Ištirti 76 pacientai, sergantys 2 tipo cukriniu diabetu. Kontrolinę grupę sudarė 24 tokio paties amžiaus sveiki asmenys. Tiriamųjų amžius buvo 60-75 metai. Pacientų įtrauktų į tyrimą amžiaus vidurkis buvo 65,54 \pm 4,37 metai (60–75 metų), iš jų 45,6 proc. (n = 31) buvo vyrai ir 54,4 proc. (n = 37) buvo moterys. Kraujo plazmos bendro cholesterolio, didelio tankio lipoproteinų cholesterolio ir trigliceridų koncentracijos buvo išmatuotos. Apskaičiuojant glomerulų filtracijos greitį (GFG), jis buvo nustatomas ir apskaičiuojamas naudojant LIL - EKI (lėtinių inkstų ligų epidemiologinis bendradarbiavimas) lygtį. Aukštos raiškos B režimo echoskopija buvo atlikta su dvipusiu skeneriu (VIVID 9 EXP) su įrengta 4,5–12 MHz linijine masyvo rele. Intimosmedijos storis (IMS) buvo matuojamas naudojant automatizuotą kraujągyslės sienelės nustatymo programinę įrangą.

Tyrimo rezultatai. Mes suskirstėme visus pacientus (sergančius 2 tipo cukriniu diabetu ir kontrolinės grupės) į 3 grupes: 1 grupė (n = 24) – pacientai, kurie neturėjo jokių papildomų aterosklerozės rizikos veiksnių, 2 grupė (n = 25) – pacientai, kurie turėjo vieną papildomą aterosklerozės rizikos veiksnį, o 3 grupė (n = 43) – pacientai turėjo du arba tris papildomus aterosklerozės rizikos veiksnius. Taikant daugialypės tiesinės regresijos analizę, atsižvelgiant į trikdančius veiksnius, IMS ir TPA buvo reikšmingai susiję su amžiumi (daugiau nei 60 metų) ($\beta = 0,359$, p < 0,0001; $\beta = 0,263$, p < 0,0001), arterine hipertenzija ($\beta = 0,041$, p = 0,003; $\beta = 0,126$, p < 0,0001), dislipidemija ($\beta = 0,066$, p = 0,0001; $\beta = 0,125$, p < 0,0001) ir LIL ($\beta = 0,054$, p = 0,003; $\beta = 0,165$, p < 0,0001) atitinkamai. Tyrimo metu nustatyti reikšmingi skirtumai lyginant kairiosios ir dešiniosios miego arterijų IMS (0,70 ± 0,16 mm, palyginti su 0,66 ± 0,13 mm, p < 0,001 atitinkamai).

Išvados. Pacientams, sergantiems 2 tipo cukriniu diabetu dislipidemija, arterinė hipertenzija ir įvairios LIL stadijos yra rizikos veiksniai sukeliantys miego arterijų plokštelių forma-

vimąsi. Taigi, ankstyva arterinės hipertenzijos, dislipidemijos ir LIL diagnostika ir savalaikis gydymas yra būtini diabetu sergantiems pacientams, kad išvengti ir sumažinti sergamumą ir mirtingumą dėl širdies ir kraujagyslių bei smegenų kraujotakos ligų, senyvo amžiaus pacientams, sergantiems cukriniu diabetu.

Reikšminiai žodžiai:

dislipidemija, lėtinė inkstų liga, arterinė hipertenzija, 2 tipo cukrinis diabetas, miego arterijų aterosklerozė