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ORIGINAL RESEARCH

Doppler study of cerebral arteries in hypercholesterolemia

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Background: Hypercholesterolemia is one of the major modifiable risk factors for atherosclerosis of the coronary and carotid arteries. Although transcranial Doppler (TCD) studies of the cerebral arteries are indicative of decreased cerebral blood flow velocities in patients with hypercholesterolemia, the number of these studies has been limited. The aim of this study was to assess the hemodynamic status of the cerebral arteries in patients with hypercholesterolemia using TCD.

Methods: In a case-control study, 60 individuals, including 30 hypercholesterolemic cases (low-density lipoprotein [LDL] > 160 mg/dL) and 30 healthy controls were enrolled. Other arterial risk factors, including diabetes mellitus, hypertension, smoking, and obesity (body mass index > 30), were evaluated and matched as well. TCD was used to assess the hemodynamics of the intracranial arteries as well as the internal carotid arteries. The mean blood flow velocity, pulsatility index, and resistance index were recorded in all the arteries.

Results: The mean blood flow velocity, pulsatility index, and resistance index of the intracranial arteries and internal carotid arteries were not significantly different between the two groups ($P > 0.05$). However, those with higher levels of LDL (>180 mg/dL) showed significantly lower mean blood flow velocity and resistance index of the internal carotid arteries than the healthy controls. In addition, individuals with high-density lipoprotein (HDL) <35 mg/dL had significantly lower mean blood flow velocity in the internal carotid arteries.

Conclusion: Hypercholesterolemia (LDL > 160 mg/dL) does not seem to have a detrimental effect on the hemodynamic status of the intracranial arteries and internal carotid arteries. However, in cases of higher LDL (>180 mg/dL) and lower HDL, decreased TCD parameters in the internal carotid arteries, as a surrogate of the peripheral arteries, are prominent.

Keywords: hypercholesterolemia, transcranial Doppler, cerebral arteries

Introduction

Cerebrovascular disease and subsequent stroke is one of the most important neurological diseases. Several modifiable (eg, hypertension, hyperlipidemia, obesity, smoking, and diabetes) and nonmodifiable (eg, gender, age, and race) risk factors for stroke have been established.[1] Hypercholesterolemia is one of the major modifiable risk factors for atherosclerosis of the coronary and carotid arteries. However, its role in the pathogenesis of stroke is unknown.[2–4] Although early epidemiological studies failed to find an association between cholesterol levels and overall stroke risk,[5,6] later investigations revealed a relationship between dyslipidemia and risk of ischemic stroke.[7–9]

Assessments of human and animal arterial vasculature revealed an impaired endothelial function in hypercholesterolemia.[10–12] In addition, transcranial Doppler

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(TCD) studies of the major cerebral arteries have shown decreased cerebral blood flow velocities in patients with familial hypercholesterolemia.[13] Nonetheless, studies of the hemodynamics of the cerebral vasculature in hypercholesterolemic patients are limited. The present study aimed at assessing the hemodynamic status of the cerebral arteries in patients with hypercholesterolemia using TCD.

Methods

In this case-control study, 60 individuals comprising 30 hypercholesterolemic cases (low-density lipoprotein [LDL] >160 mg/dL) and 30 healthy controls were enrolled in a university-affiliated hospital in Tabriz, Iran. The study was approved by the local ethics committee and written informed consent was obtained for each subject. Both groups were age- and gender-matched. Other arterial risk factors including diabetes mellitus, hypertension, smoking, and obesity (body mass index > 30) were evaluated and matched as well. Individuals who had given up smoking for more than five years were considered to be nonsmokers. TCD was used to assess the hemodynamics of the cerebral arteries (DWL®, Multi-Dop®, Germany). The standard method of using a 2 mHz probe for the intracranial arteries and a 4 mHz probe for the cervical carotids was applied in the present study. The Doppler signals were detected through the temporal window for the middle cerebral artery, anterior cerebral artery and two segments of the posterior cranial artery (PCA_1, PCA_2), through the suboccipital window for the vertebral arteries and basilar artery, and through the cervical window for the internal carotid arteries.[14] Mean blood flow velocity, pulsatility index, and resistance index were recorded in all the arteries.[15–17]

Data were presented as means ± standard deviations. Statistical analysis was performed with SPSS for Windows version 13.0 (Chicago, IL) and by using the Chi-square test, Fisher's Exact test, and independent-samples *t*-test wherever appropriate. $P < 0.05$ was considered statistically significant.

Results

Sixty individuals were included in the study, ie, 30 in the hypercholesterolemic group and 30 in the healthy control group. There were no differences in gender, age, and vascular risk factors, including hypertension, diabetes mellitus, smoking, and obesity between the groups (Table 1, $P > 0.05$). Moreover, the mean blood flow velocity, pulsatility index, and resistance index of the intracranial arteries and internal carotid arteries were not significantly different between the two groups (Table 2, $P > 0.05$).

To find out whether higher levels of LDL alter the hemodynamics of the cerebral arteries, individuals with LDL levels of less and more than 180 mg/dL were compared (Table 3). The mean blood flow velocity and resistance index of the internal carotid arteries in those with LDL > 180 mg/dL was significantly lower than that in individuals with LDL < 180 mg/dL ($P < 0.05$, Table 3). In addition, individuals with high-density lipoprotein (HDL) <35 mg/dL were compared regarding TCD indices in both groups. The analysis revealed a significant difference only in mean blood flow velocity of the internal carotid arteries.

Discussion

The hemodynamics of the cerebral vasculature in both healthy individuals and patients have been of great research interest.[18] Impaired cerebral vasomotor reactivity to L-arginine and/or CO_2 has been reported in patients with recent stroke,[19] severe internal carotid artery stenosis,[20] lacunar infarction, and high blood pressure.[21] Nonetheless, studies of the hemodynamics of the cerebral vasculature in hypercholesterolemic patients are limited. The current literature mainly focuses on the effect of lipid-lowering methods on hemodynamic alterations in the cranial arteries. Sander et al[22] and Sterzer et al[23] reported an improvement in cerebral vasoreactivity after statin administration. However, the results of PROSPER (Prospective Study of Pravastatin in the Elderly at Risk) failed to confirm this finding.[24] On the other hand, Pfefferkorn et al[25] revealed that cholesterol reduction through

Table 1 Patients' demographic data and clinical characteristics (mean ± standard deviation)

	Hypercholesterolemia group (n = 30)	Control group (n = 30)	*P* value
Gender (male:female)	14:16	14:16	1.00
Age (years)	54.66 (36–70)	51.60 (30–75)	0.55
Hypertension, n (%)	13 (43.3)	8 (26.6)	0.27
Diabetes mellitus, n (%)	4 (13.3)	5 (16.6)	1.00
Smoker, n (%)	11 (36.6)	4 (13.3)	0.07
Obesity, n (%)	8 (26.6)	5 (16.6)	0.53

Table 2 Transcranial Doppler indices of the intracranial artery (mean ± standard deviation)

Artery	Index	Hypercholesterolemia group (n = 30)	Control group (n = 30)	*P* value
MCA	MV	60.5 ± 18.8	56.2 ± 9.2	0.98
	PI	0.82 ± 0.17	0.78 ± 0.15	0.45
	RI	0.53 ± 0.08	0.51 ± 0.05	0.46
ACA	MV	46.4 ± 22.3	63.9 ± 10.1	0.86
	PI	0.76 ± 0.35	0.83 ± 0.5	0.70
	RI	0.46 ± 0.19	0.48 ± 0.14	0.45
ICA	MV	22 ± 17.9	28.7 ± 9.9	0.15
	PI	0.59 ± 0.45	0.83 ± 0.27	0.08
	RI	0.36 ± 0.26	0.51 ± 0.15	0.06
PCA1	MV	38.9 ± 12.4	37 ± 9.6	0.91
	PI	0.08 ± 0.22	0.76 ± 0.2	0.43
	RI	0.5 ± 0.11	0.49 ± 0.1	0.44
PCA2	MV	40.1 ± 13	38.6 ± 11.3	0.51
	PI	0.79 ± 0.21	0.79 ± 0.16	0.51
	RI	0.5 ± 0.11	0.53 ± 0.12	0.75
VA	MV	35.2 ± 11.6	32.9 ± 8.9	0.60
	PI	0.82 ± 0.17	0.76 ± 0.13	0.21
	RI	0.52 ± 0.06	0.51 ± 0.08	0.32
BA	MV	41.8 ± 13.2	41.2 ± 11.3	0.62
	PI	0.85 ± 0.17	0.76 ± 0.22	0.14
	RI	0.54 ± 0.06	0.49 ± 0.11	0.12

Abbreviations: MCA, middle cerebral artery; ACA, anterior cerebral artery; ICA, internal carotid artery; PCA1, first segment of posterior cranial artery; PCA2, second segment of posterior cranial artery; VA, vertebral artery; BA, basilar artery; MV, mean blood flow velocity; PI, pulsatility index; RI, resistive index.

Table 3 Transcranial Doppler indices of intracranial arteries in LDL > 180 mg/dL versus < 180 mg/dL groups (mean ± standard deviation)

Artery	Index	LDL >180 mg/dL	LDL <180 mg/dL	*P* value
MCA	MV	56.8 ± 12.56	59.1 ± 15.9	0.54
	PI	0.79 ± 0.19	0.81 ± 0.15	0.50
	RI	0.52 ± 0.09	0.52 ± 0.05	0.41
ACA	MV	44.5 ± 23.06	60.4 ± 88	0.69
	PI	0.71 ± 0.35	0.84 ± 0.46	0.23
	RI	0.44 ± 0.19	0.49 ± 0.15	0.27
ICA	MV	19.3 ± 16	28.4 ± 13.4	0.04*
	PI	0.56 ± 0.44	0.79 ± 0.34	0.055
	RI	0.34 ± 0.26	0.48 ± 0.19	0.02*
PCA1	MV	36 ± 13	38.9 ± 10	0.12
	PI	0.74 ± 0.24	0.8 ± 0.2	0.25
	RI	0.48 ± 0.01	0.51 ± 0.1	0.26
PCA2	MV	39.8 ± 15.4	39.1 ± 10.4	0.96
	PI	0.74 ± 0.23	0.82 ± 0.16	0.22
	RI	0.48 ± 0.12	0.54 ± 0.11	0.18
VA	MV	34.7 ± 10	33.6 ± 10.6	0.66
	PI	0.78 ± 0.15	0.8 ± 0.15	0.55
	RI	0.51 ± 0.05	0.52 ± 0.08	0.45
BA	MV	39.7 ± 9.1	42.30 ± 13.6	0.23
	PI	0.81 ± 0.16	0.81 ± 0.22	0.80
	RI	0.52 ± 0.06	0.51 ± 0.1	0.80

Note: *Statistically significant ($P < 0.05$).
Abbreviations: MCA, middle cerebral artery; ACA, anterior cerebral artery; ICA, internal carotid artery; PCA1, first segment of posterior cranial artery; PCA2, second segment of posterior cranial artery; VA, vertebral artery; BA, basilar artery; MV, mean blood flow velocity; PI, pulsatility index; RI, resistive index.

heparin-mediated extracorporal LDL precipitation resulted in an improvement of cerebrovascular CO_2 reactivity in patients with coronary heart disease and hyperlipidemia. Interestingly, Rubba et al[13] and Iannuzzi et al[26] noted an increasing trend in cerebral blood flow velocities after LDL apheresis in patients with familial hypercholesterolemia.

The present study showed that the hemodynamic status of the cerebral arteries, including the internal carotid arteries, was similar in healthy individuals and those with LDL > 160 mg/dL. Nonetheless, in cases of a higher cholesterol level (LDL > 180 mg/dL), decreased mean blood flow velocity and resistance index of the internal carotid artery were noted, indicating the effect of high LDL levels only on the peripheral arteries. Reduced mean blood flow velocity of the internal carotid arteries was also seen with lower levels of HDL, probably indicative of the protective effect of HDL in prophylaxis of arterial damage. Kerenyi et al[27] failed to find any significant difference between healthy controls and hyperlipidemic patients in cerebrovascular reactivity or reserve capacity after intravenous administration of acetazolamide. In a study of stroke-free Chinese individuals, hypercholesterolemia was associated with decreased blood flow velocity in the extracranial arteries, eg, the common carotid artery and internal carotid artery. However, this association was an inverse one in the intracranial arteries.[28] Nevertheless, a few studies of patients with familial hypercholesterolemia have reported contrasting results in this regard. Rubba et al[13] and Iannuzzi et al[26] found an abnormally low cerebral blood flow velocity in the middle cerebral artery prior to LDL apheresis in patients with familial hypercholesterolemia. A later study by Rubba et al[29] demonstrated lower diastolic blood flow velocities and a higher pulsatility index in the middle cerebral artery in familial hypercholesterolemic patients compared with control subjects. It seems that higher levels of LDL (about 600 mg/dL) in studies of patients with familial hypercholesterolemia have reported controversial results regarding the hemodynamic status of the cranial arteries.

Although the relationship between hypercholesterolemia and coronary and carotid artery atherosclerosis is established, its role in the pathogenesis of stroke is unknown. An ultrasound study has shown a direct relationship between lipid levels and atherosclerosis of the carotid artery.[1,30] Moreover, formation of reactive oxygen

species has been deemed to play a role in the pathogenesis of cerebral vascular dysfunction during hypercholesterolemia. Reactive oxygen species impair the response to acetylcholine, enhance superoxide activity, and lead finally to endothelial dysfunction.[31]

This study has certain limitations. It was a single-center study with a quite small sample size. A multicenter study including a large number of patients may give more concrete results. We did not exclude patients with a drug history of lipid-lowering agents. Further investigations excluding individuals on lipid-lowering agent therapy, eg, statins are recommended. Furthermore, other sources of potential bias, including anxiety disorders, were not controlled for. On the other hand, some advantages of the current study might be highlighted. We matched the hypercholesterolemic and control groups with regard to arterial risk factors, including diabetes mellitus, hypertension, smoking, and obesity. We applied two different definitions of hypercholesterolemia (LDL 160 versus 180 mg/dL) to achieve further results.

In conclusion, hypercholesterolemia (LDL > 160 mg/dL) does not seem to have a detrimental effect on the hemodynamic status of the intracranial arteries and internal carotid arteries. However, in cases of higher cholesterol levels (LDL > 180 mg/dL) and lower levels of HDL, decreased TCD parameters for the internal carotid arteries, as a surrogate for the peripheral arteries, are prominent.

Disclosure

The authors report no conflicts of interest in this work.

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