

Research Article

Influence of Statins on LDL- and HDL-Cholesterol and Plasma Fatty Acids in Elderly Japanese Ischemic Stroke Patients

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Abstract

Introduction: Stroke sometimes occurs in elderly patients who are treated with statins. The aim of our retrospective study was to investigate what influences statins had on plasma levels of LDL-C, HDL-C, triglyceride (TG) and fatty acids (FA), particularly essential FAs, in elderly Japanese acute ischemic stroke patients.

Materials and Methods: We conducted a cross-sectional study of Japanese acute ischemic stroke patients aged between 50 and 74 years admitted to our institution between Sep 2015 and Aug 2016 within 24 hours of stroke onset who took blood examination for plasma lipid levels of LDL-C, HDL-C, TG and FAs such as palmitic acid (PaA), stearic acid (StA), oleic acid (OIA), linoleic acid (LiA), dihomo-gamma-linolenic acid (DHLa), arachidonic acid (AA), eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). We assessed plasma lipid levels in patients taking statins (group S) and in patients not taking statins (group NS).

Results: One hundred forty-seven patients matched our criteria. Average age was 68 years. On arrival to the hospital, 30 patients took statins (group S) and 117 didn't (group NS). In group S and NS, LDL-C was 84.6 and 130.1 mg/dl ($p < 0.0001$), HDL-C was 50.5 and 60.3 mg/dl ($p < 0.01$), TG was 196.8 and 135.7 mg/dl ($p < 0.05$). There was no difference in plasma levels of any FAs except LiA (722.5 vs. 880.1 $\mu\text{g/mL}$, ($p < 0.001$)).

Conclusion: Plasma levels of LDL-C, HDL-C and LiA were lower in group S; however there were no differences in PaA, StA, OIA, DHLa, AA, EPA or DHA.

Keywords: Ischemic stroke; LDL-C; HDL-C

Abbreviations

LDL: Low Density Lipoprotein; LDL-C: Low Density Lipoprotein Cholesterol; HDL: High Density Lipoprotein; HDL-C: High Density Lipoprotein Cholesterol; TG: Triglyceride; PaA: Palmitic Acid; StA: Stearic Acid; OIA: Oleic Acid; LiA: Linoleic Acid; DHLa: Dihomo-Gamma-Linolenic Acid; AA: Arachidonic Acid; EPA: Eicosapentaenoic Acid; DHA: Docosahexaenoic Acid; FA: Fatty Acid; SFA: Saturated FA; PUFA: Polyunsaturated Fatty Acid; BMI: Body Mass Index; NIHSS: National Institute of Health Stroke Scale

Introduction

Previous statin trials have reported that the relative risk reduction (RRR) for stroke as a secondary endpoint was 21% with no heterogeneity between trials [1] in patients with high LDL-C level. A previous study reported that 80 mg of atorvastatin per day reduced the overall incidence of strokes and of cardiovascular events, despite a small increase in the incidence of hemorrhagic stroke [2]. Sub-analysis of previous studies reported that administration of highly purified eicosapentaenoic acid (EPA) appeared to reduce the risk of recurrent stroke in a Japanese population of hypercholesterolemic patients receiving low-dose statin therapy [3,4]. Indeed, statins are very commonly used against dyslipidemia in elderly people aged

between 50 and 74 years, however, ischemic stroke sometimes occurs in them despite oral statins. Fatty acids (FAs) are significant components of LDL, HDL and TG and it remains unknown how statins influence plasma FA levels; i.e., saturated fatty acids (SFAs) and polyunsaturated fatty acids (PUFAs) level. The aim of our retrospective study was to investigate what influences statins had on plasma levels of not only LDL-C, HDL-C and TG but also fatty acids (FAs), particularly essential FAs such as linoleic acid (LiA) of n-6 PUFAs and EPA of n-3 PUFAs, in elderly Japanese ischemic stroke patients at the onset of stroke.

Materials and Methods

Study design and subjects

We conducted a cross-sectional study of Japanese acute stroke patients aged between 50 and 74 years, who were admitted to our institution between Sep 2015 and Aug 2016 within 24 hours of stroke onset and who took blood examination for plasma lipid levels.

Exclusion

We excluded from our analysis patients who took n-3 polyunsaturated (PU) FA drugs, fibrates, or ezetimibe.

Variables

Variable we examined were plasma lipid levels of LDL-C, HDL-C,

Table 1: Patients' baseline characteristics in group S and NS.

	Group S	Group NS	p
Number (n)	30	117	
Age (median, IQR) years	68.5 (65-73)	68 (61-72)	ns
Male gender	22 (73%)	75 (64%)	ns
BMI (mean \pm SD) kg/m ²	24.3 \pm 0.8	23.5 \pm 0.4	ns
Blood pressure (mean \pm SD) mmHg	109.4 \pm 3.6	118.7 \pm 1.8	<0.05
NIHSS (median, IQR)	2 (1-3.25)	2 (1-5.5)	ns

Table 2: Plasma lipid levels and oral statins in group S and NS.

	Group S (n=30)		Group NS (n=117)		P
LDL-C (mg/dl) (average \pm SD)	84.6	-7.8	130.1 \pm 4.0		p<0.0001
HDL-C (mg/dl) (average \pm SD)	50.8	-3.1	60.3	-1.6	p<0.01
TG (mg/dl) (average \pm SD)	196.8	-21.4	135.8	-10.8	p<0.05
PaA (μ g/mL) (average \pm SD)	715.9	-42.8	781.5	-21.7	ns
StA (μ g/mL) (average \pm SD)	200.3	-11.4	222.7 \pm 5.8		0.08
OIA (μ g/mL) (average \pm SD)	709.4	-46.9	723 \pm 23.7		ns
LiA (μ g/mL) (average \pm SD)	722.5	-38.7	880.1	-19.6	p<0.001
DHLA (μ g/mL) (average \pm SD)	29.6	-2	33.1	-1	ns
AA (μ g/mL) (average \pm SD)	166.7 \pm 8.4		166 \pm 4.2		ns
EPA (μ g/mL) (average \pm SD)	76.8	-7	68 \pm 3.5		ns
DHA (μ g/mL) (average \pm SD)	129.2 \pm 8.1		136.5 \pm 4.1		ns
Stains	Rosuvastatin; 9		none		
	Pitavastatin; 9				
	Atorvastatin; 6				
	Pravastatin; 6				

TG and FAs such as palmitic acid (PaA) and stearic acid (StA) of SFAs, oleic acid (OIA) of n-9 PUFA, LiA, dihomo-gamma-linolenic acid (DHLA) and arachidonic acid (AA) of n-6 PUFA, EPA and docosahexaenoic acid (DHA) of n-3 PUFA.

Evaluation

We assessed baseline patients' characteristics such as age, gender, BMI and NIHSS, and plasma lipid levels in patients taking statins (group S) and in patients not taking statins (group NS).

Statistical analysis

Age and NIHSS were expressed as median and interquartile range (IQR) and compared by Mann-Whitney's U test. Other continuous variables, expressed as mean \pm SD, were compared by unpaired Student's t test. Categorical data were compared by using the Chi square test or the Fisher exact test. A probability of less than P=0.05 was considered statistically significant. The JMP (version 13.0.0) program was used to perform the statistical analysis.

Results

During study period, 167 acute ischemic stroke patients aged between 50 and 74 years were admitted to our institution and 13

patients were excluded from analysis because of no blood examination of plasma FAs and subsequently 7 patients were excluded because of oral n-3 PUFA drugs or ezetimibe. Finally, one hundred forty-seven patients matched our criteria and were analyzed. Their age (median, IQR) was 68 years (63-72), male gender was 97 (66%), their BMI (mean \pm SD) was 23.7 \pm 4.3 kg/m², blood pressure was 116.8 \pm 19.8 mmHg, NIHSS (median, IQR) was 2 (1-5). As standard lipid examination, LDL-C, HDL-C and TG were 120.8 \pm 46.5, 58.3 \pm 17.3 and 148.2 \pm 119.2 mg/dl. As SFAs, PaA and StA were 768.1 \pm 235.1 and 218.1 \pm 62.9 μ g/mL. As n-9 PUFA, OIA was 720.2 \pm 255.8 μ g/mL. As n-6 PUFAs, LiA, DHLA and AA were 848.0 \pm 220.7, 32.4 \pm 11.3 and 166.2 \pm 45.6 μ g/mL. As n-3 PUFAs, EPA and DHA were 69.8 \pm 38.2 and 135.0 \pm 44.2 μ g/mL. Their average EPA level wasn't high. On arrival to the hospital, 30 patients (20.4%) took statins (group S) and 117 didn't (group NS). There were no differences of patients' baseline characteristics between group S and NS except blood pressure (Table 1). In group S, strong (3rd generation) statins was used in 80% (Table 2). In group S and NS (Table 2), LDL-C was 84.6 and 130.1 mg/dl (p<0.001), HDL-C was 50.5 and 60.3 mg/dl (p<0.01), TG was 196.8 and 135.7 mg/dl (p<0.05), PaA was 715.9 and 781.5 μ g/mL (ns), StA was 200.3 and 222.7 μ g/mL (ns), OIA was 709.4 and 723.0 μ g/mL (ns), LiA was 722.5 and 880.1 μ g/mL (p<0.001), DHLA was 29.6 and 33.1 μ g/mL (ns), AA was 166.7 and 166.0 μ g/mL (ns), EPA was 76.8 and 68.0 μ g/mL (ns), DHA was 129.2 and 136.5 μ g/mL (ns). There were no differences in plasma levels of any FAs except LiA in both groups. There were no differences of SFAs nor essential FAs except LiA level between two groups. In both groups, EPA level wasn't high and AA level wasn't low.

Discussion

Our results demonstrated that EPA level wasn't high in patients with nor without statin and that there were no differences of any FAs including EPA except LiA in both groups, although LDL-C and HDL-C level was lower in patients with oral statin.

Previous statin trials have reported that the relative risk reduction (RRR) for stroke as a secondary endpoint was 21% with no heterogeneity between trials [1]. Each 10% reduction in LDL-C was estimated to reduce the risk of all strokes by 13.2% (95% CI: 4.8-20.6) [1]. Statins have not been shown to prevent recurrent stroke in patients with prior stroke, although a previous study reported that, in patients with recent stroke or TIA and without known coronary heart disease, 80 mg of atorvastatin per day reduced the overall incidence of strokes and of cardiovascular events, despite a small increase in the incidence of hemorrhagic stroke [2].

Fatty acids have relation to cardiovascular risks [3,5-7]. Sub-analysis of previous studies reported that administration of highly purified eicosapentaenoic acid (EPA) appeared to reduce the risk of recurrent stroke in a Japanese population of hypercholesterolemic patients receiving low-dose statin therapy [3,4].

Our results demonstrated that statins didn't have influences on plasma levels of SFA nor PUFA including EPA, although cholesterol synthesis was significantly impaired. Lower LDL-C level in group S indicated that patients in group S really had taken statins prior to stroke onset. It may be why statins haven't been clearly shown to prevent stroke primarily or secondarily. Essential FAs people can't

synthesize are driven from diet. Therefore, there were no differences in essential FAs levels between patients with and without statins, and this was because diet before stroke onset may be almost the same in both groups. To prevent stroke primarily or secondarily, diet should be changed or improved in viewpoints of essential FAs.

The present study has several important limitations. The investigation was conducted in a single department at a single comprehensive stroke center, and the number of patients was small. Patients on statins prior to their stroke might be inherently different from patients not on statins prior to their stroke, because the present study was not a case-control but a retrospective cross-sectional study and it was unknown why patients didn't take statins prior to their stroke. Indeed, stain effects on essential FAs are not well known, but statins alone couldn't increase EPA level [3,4]. Furthermore, statin adherence prior to stroke onset wasn't measured. Therefore, the present study can't demonstrate statin effects or influences on essential FAs, particularly EPA of n-3 PUFA, however statin probably can't increase nor decrease EPA but also increase nor decrease AA.

Conclusion

Plasma levels of LDL-C, HDL-C and LiA were lower in group S; however there were no differences in plasma levels of PaA and StA of SFAs, OIA of n-9 PUFA, DHLA and AA except LiA of n-6 PUFA of essential FAs, EPA and DHA of n-3 PUFA of essential FAs.

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