ORIGINAL ARTICLE

Dietary Fat Intake and Changes in Tunica Intima-Media Thickness Internal Carotid Artery in Post Ischemic Stroke Patients

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ABSTRACT

Background: Carotid intima-media thickness (cIMT) is one of the markers for atherosclerosis associated with the risk of stroke. Dietary fat intake is a risk factor for both atherosclerosis and stroke. Correlation of dietaryfat intake in post ischemic stroke patients with changes in cIMT has not been widely published.
Aim: To analyze correlation between dietary fat intake and changes in cIMT in post ischemic stroke patients.
Method: This is a prospective cohort study conducted in neurology clinic, Dr. Kariadi General Hospital, Semarang. Subjects were60 post ischemic stroke patients. cIMT was examined at baseline with a 6 month follow up period. The intake of fat (total fat), Saturated Fatty Acids (SFA), Monounsaturated Fatty Acids (MUFA) and polyunsaturated fatty acids daily (PUFA) was measured using semi quantitative Food Frequency Questionnaire. Demographic data and risk factors for stroke were documented during recruitment of subjects. Examination ofblood pressure, serum lipid profile (total cholesterol, LDL-C, HDL-C, TG), GD I, GD II, and HbA1c were also performed at baseline with a 6 month follow-up period. The relationship between dietary fat intake and progression of cIMT were analyzed using correlation, Pearson Chi-square, Fisher, and logistic regression. The analysis was significant if the p value <0.05.
Result: The mean age of subjects was 61.2 $\pm$ 8.2 years, 61.6% were male, with a mean BMI of 22.3 $\pm$ 2.2 kg / m^2. Total daily dietary fat intake of > 30% of total energy was found in 58.3% of subjects. SFA intake of $\geq$10% of total energy was found in 71.7% of subjects. PUFA intake <6% of total energy was found in 61.7% of subjects. There is an increase in mean of cIMT thickness over 6 months, with mean of cIMT at baseline was 0.73 $\pm$ 0.24 mm and was increased to 0.82 ±0.25 mm at 6 months follow-up. Total fat intake was positively correlated with ΔcIMT (r = 0.661, p = <0.001). While the dietary intake of PUFA negatively correlated with ΔcIMT (r = - 0.859, p = <0.001).
Conclusion: There is a positive correlation between total daily dietary fat intake and changes in cIMT. The intake of PUFA is negatively correlated with the changes in cIMT. People with total daily fat intake> 30% of total energy had 6.17 times higher risk for an increase of cIMT> 0.1 mm in 6 months. The intake of polyunsaturated fatty acids daily (PUFA) <6% of total energy had 8.92 times the risk of increased cIMT> 0.1 mm in 6 months.
Keywords: Fat intake, intima-media thickness (IMT) of the carotid arteries, atherosclerosis, post ischemic stroke

INTRODUCTION

Stroke is a leading cause of death and disability. Stroke has a very high incidence rate. It is estimated that 6.5 million people die per year because of stroke in the world.[1]In Indonesia, according to data from Ministry of Health, the prevalence of stroke was increased from 8.3 per 1000 population in 2007 to 12.1 per 1000 population in 2013.[2,3]The most common type is ischemic stroke, accounts for 87% of all stroke[4].Atherosclerosis in major blood vessels, particularly in the middle cerebral artery is the most common cause of ischemic stroke[5].

Measuring tunica intima-media thickness of the carotid artery / Carotid Intima-Media Thickness (cIMT) is examination used to assess the risk of atherosclerosis and cardiovascular disease.[6]An increase in intima-media thickness of the common carotid artery and internal carotid artery is associated with an increased risk of ischemic stroke and is an independent predictor of recurrent ischemic stroke events. Every additional 0.1 mm of CCA IMT thickness increases the possibility of recurrent ischemic stroke by 18%[7].

The mechanism of atherosclerosis is very complex and is influenced by a variety of risk factors, either irreversible or potentially modifiable. Evidence from observational and interventional studies showed that Dietary Fat intake has been recognized as a risk factor for ischemic heart disease[8,9]. However, the relationship between dietary fat intake with ischemic stroke remains unclear. There are controversial results among studies and there is still no consensus about the relationship between dietary fat intake with ischemic stroke.[10-13] The aim of this prospective cohort study is to analyze the relationship between dietary fat intake post ischemic stroke patients with progression of cIMT.

SUBJECTS AND METHODS

Population and subjects: This is a prospective cohort study conducted in neurology clinic, Dr. Kariadi General hospital. Recruitment of subjects was using consecutive sampling method. Subjects were post ischemic stroke patients, recruitedlessthan a month after stroke onset. The inclusion criteria include age 40-70 years old and ischemic stroke, evidenced by CT scan of the head. Exclusion criterias include patients who use antilipid drug, aphasia, use NGT for food intake, and those with history of heart disease. 102 subjects who met the criteria signed informed consent. Baseline examination was conducted from January to December 2013. Follow-up investigation was conducted 6 months after baseline investigation. 60 subjects completed all study procedures, while52 subjects who dropped out (Figure 1). All research respondents were requested to give written informed consent and patient's

identity was confidential. This research was approved by The Health Research Ethics committee of Faculty of Medicine Diponegoro University / RSUP Dr. Kariadi Semarang number 656/EC/FK-RSDK/2015.

Data collection characteristics of subjects at baseline: Subjects who already sign informed consent undergo the history and physical examination. Demographic data and stroke risk factors such as hypertension, diabetes mellitus, dyslipidemia, and smoking history as well as the treatment of the secondary prevention of stroke obtained through the patient's history and medical records. Physical examination of weight and height for measuring BMI (body mass index) and blood pressure were also documented.

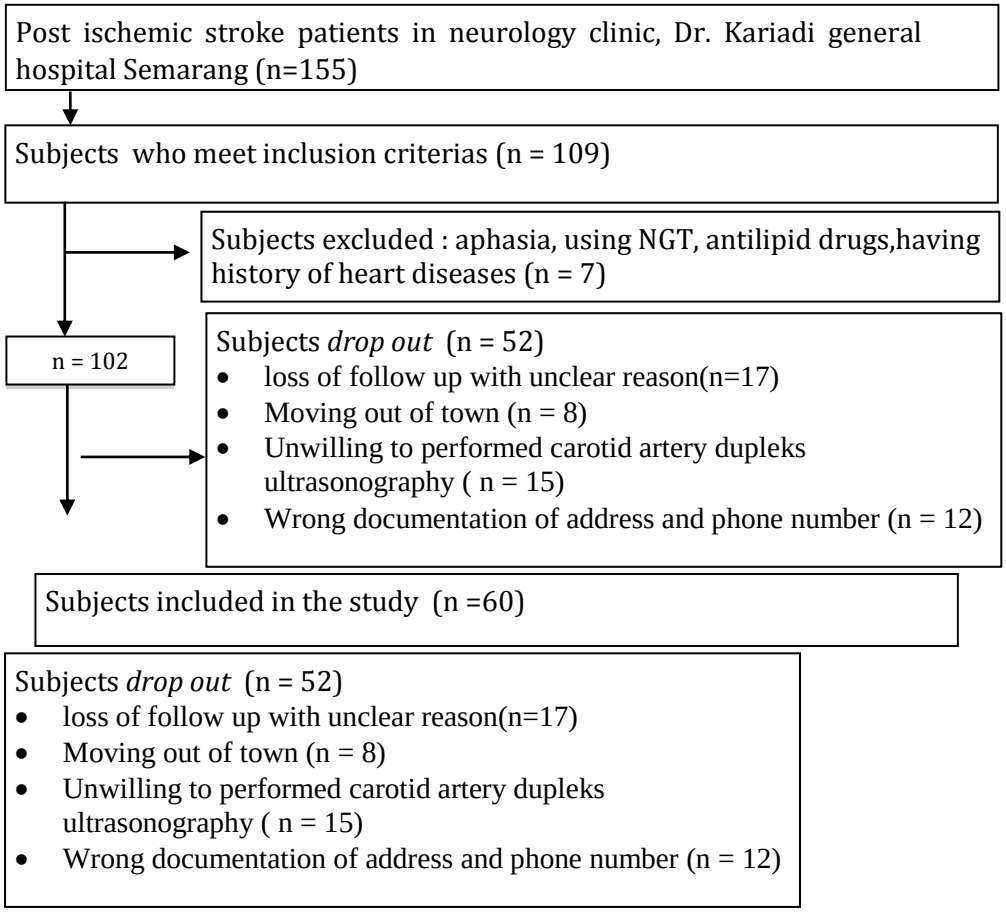
Laboratory tests and follow-up: A laboratory examination of serum lipid profile (total cholesterol, LDL-C, HDL-C, TG), Blood Glucose Level I (Fasting), Blood Glucose Level II (2 hour post prandial), and HbA1c performed at baseline and 6 months follow-up.

Assessment of dietary food intake: Dietary intake of fat (total fat), saturated fatty acids (SFA), monounsaturated fatty acids (MUFA) and Polyunsaturated Fatty Acids (PUFA) is measured by FFQ (Food frequency questionnaire) semi quantitatively.[14] FFQ assessment was performed by nutritionists on their visitation to subject's houses. In the FFQ were documented how often, on average, subjects consume certain foods that are in the list. Nutritionists weigh food at home whenever applicable. FFQ assesment were performed three times, at baseline and 6 months follow-up. The nutritional intake of the subjects were the average of two times examination. Data were then processed using Nutrisoft to determine the quantity of dietary fat intake. The validity of the FFQ has been widely evaluated by previous studies.[15-17]

Measurement of intima-media thickness of the carotid artery (cIMT / Carotid Intima-media thickness): The thickness of the carotid artery intima-media / cIMT was assessed by carotid duplex ultrasound with high resolution B-mode (Siemens soniline Omnia serial number FBE 0322 ®) in the Department of Radiology, dr. Kariadi general hospital, Semarang. Measurement of right and left Internal carotid artery IMT was performed 1 cm distalcarotid bifurcation in mm.[18]Value is determined as the average of right and left Cimt[7].All ultrasound examinations performed by radiologist sonographer blindedly. cIMT measurement were performed twice, at baseline and 6 months follow-up. Delta cIMT is defined as the difference between carotid duplex ultrasound examination of 6 months follow-up and baseline.

Statistical analysis: Data analysis was performed using Statistic's software.Normality test using the Kolmogorov-Smirnov test. The relationship between fat intake and progression of cIMT were analyzed using correlation test in accordance with the distribution of the data, the Pearson Chi-square, Fisher, and logistic regression. The analysis was significant when the p value <0.05.

Figure 1. Recruitment of subjects



RESULTS

Out of 155 post ischemic stroke patients, only 102 subjects met the criteria and signed informed consent. 52 subjects dropped out for various reasons.60 subjects who completed all procedures.

The mean patient age was 61.2± 8.2 years, the majority of male (61.6%), the mean BMI is normal is 22.3±2.2 kg/m^2. Cardiovascular risk factors often found in the subjects was history of dyslipidemia (55.0%) and a history of smoking (46.6%).

Fat intake was calculated based on a percentage of the total energy. The mean percentage of total fat to total energy was 30.7±.8%, SFA 13.4±4.4%, MUFA 5.0±1.9%, and PUFA 5.6±2.3%. A total of 35 (58.3%) subjects consumed daily total fat exceeds the recommendation and 43 (71.7%) consumed daily SFA exceeds the recommendation.

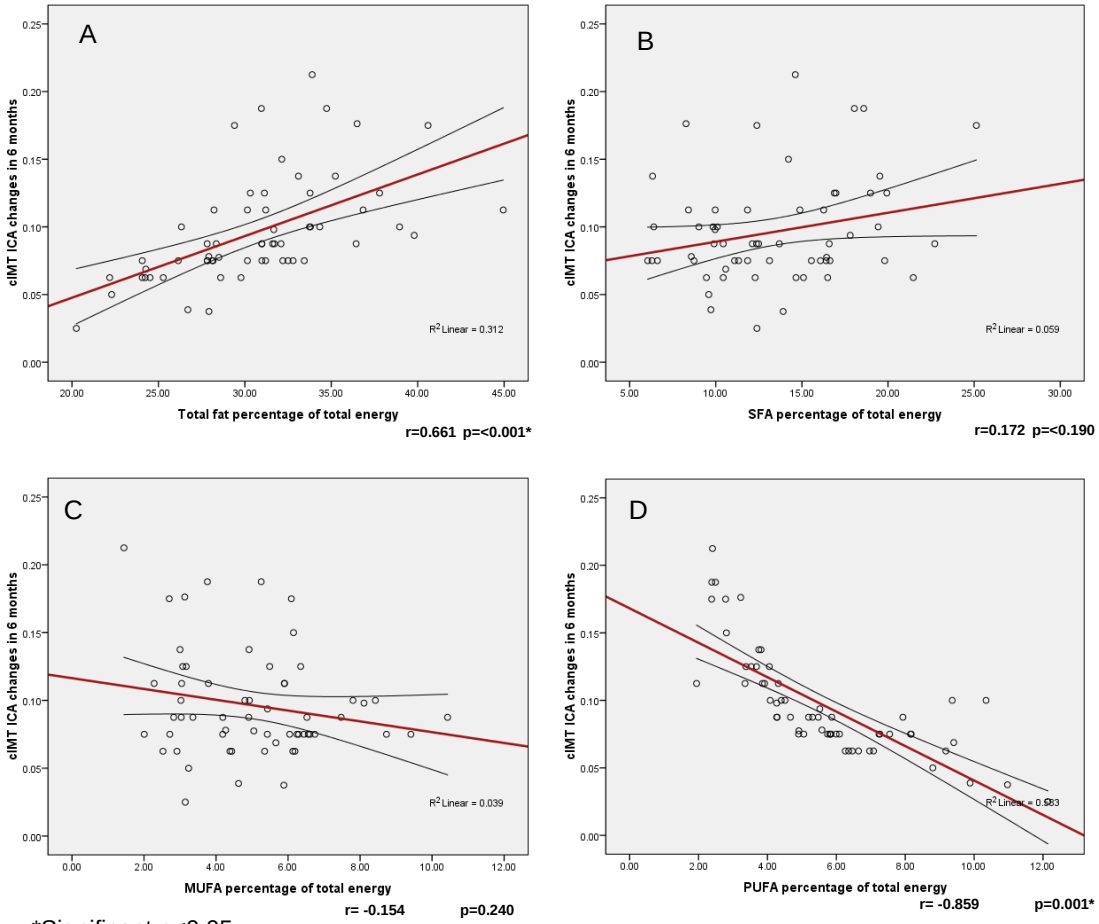
Based on examination of blood serum baseline, subjects had normal lipid profile and blood glucose level. Based on carotid Doppler ultrasound examination, the mean IMT of internal carotid artery at baseline was from 0.73±0.24 mm to 0.82 $\pm$ 0.25 mm sixth month after baseline examination. Thus the average addition of Internal Carotid Artery IMT for 6 months was 0.09±0.04 mm. A total of 19 (31.7%) subjects experienced internal carotid artery additional IMT> 0.1 mm in 6 months (Table 1).

This study showed a positive correlation between dietary fat daily intake with ΔcIMT, which is statistically significant (r = 0.661; p <0.001). The daily intake of polyunsaturated fatty acids (PUFA) was negatively correlated with ΔcIMT, which is statistically significant (r = -0.859; p <0.001). Daily intake of SFA positively correlated to the ΔcIMT, while daily intake MUFA negatively correlated to the ΔcIMT but not statistically significant (Figure 2).

Bivariate statistical analysis showed that the risk factors that affect the progression of IMT for 6 months are high LDL levels, high total fat intake, and low intake of PUFA (Table 2).

Logistic regression multivariate analysis were used to analyze the effects of sex, hypercholesterolemia, low HDL levels, low intake of dietary fiber, high total fat intake, and the intake of PUFA on the thickness of the intima-media internal carotid artery. In this study it was found that low HDL levels (p = 0.041; RR = 0.056) is a factor that independently affect the increased intima-media thickness of the internal carotid artery (Table 3).

Figure 2. The correlation between total fat intake with ΔcIMT (A), SFA with ΔcIMT (B), MUFA with ΔcIMT (C), PUFA with ΔcIMT (D).



*Significant p<0.05

Table 1. Characteristics of post ischemic stroke patients after ischemic stroke

Variable	*Mean*± SD/ Median (min-maks)	n (%)
Age (year)	61.2 ± 8.2	
Male		37 (61.6)
BMI (kg/m^2)	22.3 ± 2.2	
History of smoking		28 (46.6)
Diabetes mellitus (%)		6 (10.0)
Hypertension (%)		17 (28.3)
History of dyslipidaemia (%)		33 (55.0)
Dietary fat intake		
Total fat (% total energy)	30.7 ± 4.8	
Total Fat > 30% total energy		35 (58.3)
SFA (% total energy)	13.4 ± 4.4	
SFA ≥ 10% total energy		43 (71.7)
MUFA (% total energy)	5.0 ± 1.9	
MUFA < 2% total energy		4 (6.7)
PUFA (% total energy)	5.6 ± 2.3	
PUFA < 6% total energy		37 (61.7)
Cholesterol (mg/ day)	194.4 ± 86.5	
Lipid Profile *baseline*		
Total colesterol total (mg/dl)	166.1 ± 45.1	
LDL colesterol (mg/dl)	135.4 ± 44.6	
HDL colesterol (mg/dl)	46.4 ± 10.4	
Trigliseryde (mg/dl)	125.7 ± 66.3	
Glucose level *baseline*		
Blood Glucose level I (fasting)	97 (81-357)	
Blood Glucose Level II (2 hour post prandial)	129 (86-548)	
HbA1C	5.5 (2.8-13)	
cIMT ICA *baseline* (mm)	0.73 ± 0.24	
cIMT ICA 6 bulan (mm)	0.82 ± 0.25	
Delta cIMT ICA (mm)	0.09 ± 0.04	
Delta cIMT ICA >0.1 mm / progresif		19 (31.7)

Table 2. The influence of risk factors for the progression of carotid IMT for 6 months

Risk Factor	**Progressivity carotid artery 6 months after onset**		***p***	**RR (95%CI)**
	Progressive (> 0.1 mm) n = 19	**Unprogressive (≤0.1 mm) n=41**		
Age				
>60 y.o	9 (27.3%)	24 (72.7%)	0.419[α]	0.64 (0.21 – 1.90)
≤ 60 y.o	10 (37.0%)	17 (63.0%)		
Gender				
Male	14 (37.8%)	23 (62.2%)	0.192[α]	2.19 (0.66 – 7.22)
Female	5 (21.7%)	18 (78.3%)		
Overweight/obesity				
Yes	1 (33.3%)	2 (66.6%)	0.949[β]	1.08 (0.09 – 12.74)
No	18 (31.6%)	39 (68.4%)		
Smoking				
Yes	10 (35.7%)	18 (64.3%)	0.528[α]	1.42 (0.47 – 4.23)
No	9 (28.1%)	23 (71.9%)		
Hypertension				
Yes	5 (29.4%)	12 (70.6%)	0.813[α]	0.86 (0.25 – 2.93)
No	14 (32.6%)	29 (67.4%)		
Diabetes mellitus				
Yes	2 (33.3%)	4 (66.7%)	0.926[β]	1.08 (0.18 – 6.53)
No	17 (31.5%)	37 (68.5%)		
Dyslipidemia				
Hypercolesterolemia				
Yes (> 200 mg/dl)	11 (42.3%)	15 (57.7%)	0.121[α]	2.38 (0.78 – 7.23)
No	8 (23.5%)	26 (76.5%)		
Hypertrigliserydemia				
Yes (> 150 mg/dl)	2 (18.2%)	9 (81.8%)	0.287[β]	0.42 (0.08 – 2.16)
No	17 (34.7%)	32 (65.3%)		
Low HDL level				
Yes (< 40 mg/dl)	4 (20.0%)	16 (80.0%)	0.170[α]	0.42 (0.12 – 1.48)
No	15 (37.5%)	25 (62.5%)		

High LDL level				
Yes (> 160 mg/dl)	11 (61.1%)	7 (38.9%)	0.001*	6.68 (1.97 – 22.65)
No	8 (19.0%)	34 (81.0%)		
Total fat intake				
> 30% total energy	16 (45.7%)	19 (54.3%)	0.006*	6.17 (1.56 – 24.48)
≤ 30% total energy	3 (12.0%)	22 (88.0%)		
SFA intake				
≥ 10 % total energy	15 (34.9%)	28 (65.1%)	0.394 [α]	1.74 (0.48 – 6.28)
< 10 % total energy	4 (23.5%)	13 (76.5%)		
MUFA intake				
< 2 % total energy	1 (25.0%)	3 (75.0%)	0.767 [β]	0.70 (0.07 – 7.24)
≥ 2 % total energy	18 (32.1%)	38 (67.9%)		
PUFA intake				
< 6 % total energy	17 (45.9%)	20 (54.1%)	0.003*	8.92 (1.82 – 43.68)
≥ 6 % total energy	2 (8.7%)	20 (91.3%)		

[α]Chi square test, [β]Fisher test, *Significant p<0.05

Table 3. Logistic regression between risk factors for the progression of carotid IMT

Variable	**Progressivity carotid artery 6 months**		**Bivariat**	**Multivariat**	
	Progressive (>0.1 mm)	**Unprogresive**	***p-value***	***p-value***	**RR (95%CI)**
Demography					
Age (>60 years old) (n=33)	9 (27.3%)	24 (72.7%)	0.419[α]		
Gender(Male) (n=37)	14 (37.8%)	23 (62.2%)	0.192 [α]	0.132	6.627 (0.567-77.403)
Vascular Risk Factor					
BMI (*overweight/ obese*) (n=3)	1 (33.3%)	2 (66.6%)	0.949[β]		
Smoking (n=28)	10 (35.7%)	18 (64.3%)	0.528 [α]		
Hypertension (n=17)	5 (29.4%)	12 (70.6%)	0.813 [α]		
Diabetes Melitus (n=6)	2 (33.3%)	4 (66.7%)	0.926 [β]		
Dyslipidemia					
hypercholesterolemia(n=26))	11 (42.3%)	15 (57.7%)	0.121 [α]	0.837	1.256 (0.144-10.991)
Hypertrigliserydemia (n=11)	2 (18.2%)	9 (81.8%)	0.287 [β]		
Low HDL (n=20)	4 (20.0%)	16 (80.0%)	0.170 [α]	0.041*	0.056 (0.003-0.888)
High LDL (n=18)	11 (61.1%)	7 (38.9%)	0.001* [α]	0.702	0.612 (0.049-7.596)
Dietary intake					
High total fat (n=35)	16 (45.7%)	19 (54.3%)	0.006* [α]	0.453	2.530 (0.224-28.545)
High SFA (n=43)	15 (34.9%)	28 (65.1%)	0.394 [α]		
Low MUFA (n=4)	1 (25.0%)	3 (75.0%)	0.767 [β]		
Low PUFA (n=37)	17 (45.9%)	20 (54.1%)	0.003* [α]	0.723	1.588 (0.124-20.376)

[α]Chi square test, [β]Fisher test

DISCUSSION

Age is an independent risk factor for an increase in cIMT particularly in the elderly. Normally people have cIMT approximately 0.5±0.8 mm, which will increase significantly with age, especially over 40 years without being affected by the risk factors.[19]This study showed that age had influence on cIMT which is a marker of atherosclerosis. The mean age was 61.2± 8.2 years. Most of the study subjects were males 37 (61.6%). Most studies comparing subclinical atherosclerosis and between men and women reported a higher prevalence in men than in women[20].

Risk factors for stroke which are found the most in this study includes the history of dyslipidemia and smoking. Only few subjects have diabetes mellitus and hypertension. Increased cIMT was reported on a study of stroke patients with diabetes mellitus, the Insulin Resistance Atherosclerosis Study. The research proves the increase in cIMT between diabetic and non-diabetic[21]. Diabetes affects atherosclerosis through mechanisms of hyperglycemia, decreased production of nitric oxide, induced vasoconstriction, increased stress oxide, which all lead to endothelial dysfunction and promote atherosclerosis[22]. History of smoking was found in almost half of the study subjects, even though during the course of the study subjects no longer smoking. Smoking causes progressivity of aterosclerosis particularly smoking at a young age[23]

In this study, the dietary intake of fat is a variable that consists of the intake of total fat, SFA, MUFA and PUFA. Each gram of fat components produces 9 calories per gram.[24]Analysis of the daily nutrient intake by FFQ showed that the percentage of total fat consumption to total energy in each subjects was 30.7±4.8%. This value is above recommendation (<30% of total energy). A total of 35(58.3%) subjects have daily consumption of total fat exceeds WHO recommendations. The mean percentage of saturated fat intake (SFA) of total energy intake was 13.4± 4.4%, this value is also higher than a recommendation based on the reference (<10%). A total of 43(71.7%) subjects have daily consumption of saturated fat exceeds the recommendations. These results indicate that the condition of post-stroke patients did not reduce fat consumption. This might be due to the high consumption patterns of fat before the stroke is maintained[25].

Result of cIMT measurement on the study subjects showed a rise during six months, from a mean of 0.73±0.24 mm at baseline investigation to a mean of 0.82±0.25 mm on a 6-month investigation. Mean additional / ΔcIMT for 6

months was 0.09 ± 0.04 mm. Study conducted by Tsivgoulis et al with the subject of post-first stroke patients, comparing cIMT among patients who experienced recurrent stroke patients with those without recurrent stroke. The study results showed mean cIMT of patients with recurrent stroke was 1.09±0.94 mm, thicker compared with patients without recurrent stroke of 0.86±0.86 mm.(7) The results of these studies support the findings of our study indicate that patients with post-stroke has tended abnormal cIMT. In a meta-analysis studies with a total of 37,000 study subjects showed that 0.1 mm increased in cIMT resulted in 13-18% increased risk of having a stroke[26].

The results of this study support the importance of carotid duplex ultrasound measurement as a marker of atherosclerosis, particularly in post-stroke patients. Carotid duplex ultrasound examinations may be performed in post-stroke patients periodically to monitor changes in the thickness of the carotid artery. Use of cIMT for determining atherosclerosis has been recognized by the FDA (Food and Drug Administration) States and the European Agency for the Evaluation of Medical Products. However, examination of cIMT is still not widely known among clinicians that have not been used.[27]

Analysis of Correlation between cIMT and each component of fat intake showed that the intake of total fat and saturated fatty acids (SFA) positively correlated to ΔcIMT. While the intake of polyunsaturated fatty acids (PUFA) and monounsaturated fatty acids (MUFA) are negatively correlated with it. Statistically significance correlation shown in high total fat and low PUFA intake to ΔcIMT.

Study performed by Merchant et al supported this research that the SFA consumption is associated with cIMT thickening on the subject with and without alcoholism.(11) Research by Tell et al and Mozaffarian et al also reported the same results that SFA is positively correlated with cIMT.[12,13] However Merchant et al does not support the evidence that total fat consumption is related cIMT thickening. This is in contrast to our study, indicating that total fat intake was positively correlated strongly with ΔcIMT ($r = 0.661$; $p = <0.001$). Fat and SFA intake is associated with atherosclerosis risk through increased concentrations of total cholesterol, LDL, and triglycerides. This further reduces atherogenic lipoproteins that will reduce cholesterol in the arterial intima layer and inhibit the progression of atherosclerotic lesions.

The results of this study showed that PUFA was negatively correlated with ΔcIMT. These findings are similar to those reported by Mozaffarian et al, Tell et al and Wolfe et al.[12,13,28] Wolfe et al reported that African monkeys with high consumption of PUFA less experienced cIMT thickening significantly than those which consume SFA. However, this result is not supported by research Merchant et al stated that PUFA are not associated with cIMT.

The correlation between fat intake and cIMT was expressed as a percentage of total energy. This means that the proportion of fat intake to the overall total energy consumed (including carbohydrates and proteins) was associated with progression of atherosclerosis. So in a set pattern of intake, fat percentage of total energy is important to note. This study supports the role of fat intake had a greater influence on the progression of atherosclerosis than expected, particularly in post ischemic stroke patients.

Based on bivariate test, the factors that influence the change of cIMT for 6 months are high LDL levels, high total fat intake, and low intake of PUFA. Abnormal criteria of serum lipid profile was using the benchmark National Cholesterol Education Panel - Adult Treatment Panel III (NCEP-ATP III).[29] Someone with LDL> 200 mg / dL had 6.68 times increased risk of progressive cIMT. Daily total fat intake> 30% of total energy had 6.17 times increased risk of progressive cIMT. While the PUFA intake of <6% of total energy has risk 8.92 times increased risk of progressivecIMT. These results indicate the role of fat intake to changes in cIMT in post ischemic strokepatients. Modifications of nutrition in general and fat intake is particularly important in post ischemic stroke patients.

Multivariate logistic regression analysis showed levels of HDL <40mg/dl is a factor that independently influence the changes in the thickness of carotid intima-media for 6 months in patients after ischemic stroke. According to the research findings of research in Greece. In that study found that subjects with high HDL levels are inversely related to cIMT ($r = -0.42$; $p = 0.03$).[30] The protective role of HDL via reverse cholesterol transport, i.e., by reducing the content of cholesterol in the atherogenic plaques in the blood vessels and tissue cells leading to the liver for excretion into the gallbladder. Additionally HDL has antioxidant function, anti-inflammatory, antithrombotik, and process improvement of endothelial dysfunction to protect them from the development of atherosclerosis[31].

There are some limitations to this study. First, the absence of an assessment of physical activity during the study subjects.Second, the lack of comparison with normal subjects (without history of stroke). Thirdly, the assessment of food intake should be performed only twice, namely at the baseline and follow-up 6 months later. Fluctuations in the period between the eating habits that can be changed because of social, economic, and psychological are not taken into account.

CONCLUSION

There is a positive correlation between total fat daily intake with ΔcIMT. The intake of polyunsaturated fatty acids daily (PUFA) were negatively correlated with ΔcIMT. Total daily fat intake > 30% of total energy resulted in 6.17 times increased risk of having increased cIMT> 0.1 mm in 6 months. The intake of polyunsaturated fatty acids daily (PUFA) <6% of total energy resulted in 8.92 times increased risk of having increased cIMT> 0.1 mm in 6 months.

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