The Variation in Cholesterol and Triglycerides Levels and the Risk for Stroke in First Degree Relatives of Stroke Patients

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Cerebrovascular diseases have become a leading cause of mortality and major invalidity throughout the world in the last years. The levels of cholesterol and triglycerides are among the modifiable risk factors for stroke. The intima media thickness (IMT) is a very good marker for subclinical atherosclerosis and also for predicting future cardio- and cerebrovascular events. The aim of this study was to determine correlations between the lipid profile and the value of the intima media thickness as a risk factor for stroke in first degree relatives of stroke patients. We evaluated a total of 176 subjects, selected by well defined criteria, divided into three groups: stroke patients, first degree relatives of stroke patients and a healthy control group. We measured weight, height and body mass index, the levels of cholesterol and triglycerides, and IMT by cervical ultrasound mode B, at the common carotid artery (CCA) and internal carotid artery (ICA) bilaterally. The mean values of lipids were in the normal range. However, in the stroke group, both cholesterol and triglyceride levels were increased compared to the other groups. The triglycerides level positively correlated with IMT in the CCA in both control and stroke patients, but this was not the case for cholesterol levels. Also, the increase in IMT in stroke patients correlated with an increase in IMT of their relatives. Further research is needed in order to elaborate a screening algorithm for primary prevention of stroke in first degree relatives of stroke patients.

Keywords: cholesterol, triglyceride, intima media thickness, stroke

Stroke is one of the leading causes of mortality and morbidity everywhere in the world, representing the most important cause of long-term disability in the middle aged and old population. Approximately 4.4 million people die from the consequences of stroke each year, which accounts for around 9% of all deaths worldwide, 88% of these in people over 65 years of age [1]. In simpler terms, for most Western countries, every 8-10th death is caused by a stroke, the incidence increases with age and the risk doubles for every decade after the age of 50 [2]. Studies show that the prevalence of stroke is higher among first-degree relatives of stroke patients and that an increased risk for stroke may be explained by the heritability of hypertension [3].

Atherosclerosis is a vascular disease involved in the etiology of 60-70% of ischemic strokes. It is considered to be an infiltrative and degenerative process that associates both lipid deposits in the intimate and a fibrous reaction. The first lesions of atherosclerosis occur in the second decade of life, but this does not become symptomatic until after the sixth decade of life [4]. Atherosclerosis is thought to be a multifactorial disease, modulated by classical risk factors (cholesterol, triglycerides, hypertension, smoking, obesity) but it can be quantified from the subclinical stage by markers such as carotid intima-media thickness (IMT), ankle-brachial index, arterial calcification score and arterial stiffness [5,6].

Data from the literature highlights the link between the IMT and ischemic stroke [7]. The growth of the intima-media layer places the patient at risk of developing a transient ischemic stroke or a stroke that is constituted or even recurrent [8,9]. Several studies have shown promising results on the role of the intima-media thickness as an independent risk factor for ischemic stroke and other cardiovascular events [10,11].

Experimental part

The aim of this study was to identify direct and indirect correlations between some already known cardiovascular risk factors and ultrasound measurements, in order to predict stroke and vascular risk in first degree relatives of patients with stroke, as some authors have already suggested [12]. Our research focused on 3 groups: patients with atherotrombotic ischemic stroke (already diagnosed clinically and with CT scan), one of first degree relatives of the stroke patients (mainly their children, adults without any known risk factors) and one of healthy individuals (without any known risk factors). Exclusion criteria for all groups were any embolic conditions, the presence of diabetes, atheroma plaques, stenosis or occlusion in the carotid arteries or a value of the IMT more than 1.5 mm. All subjects before being examined were informed of the research method and signed an informed consent.

IMT was examined with the Siemens Accuson X300 system using a 7.5 MHz linear probe with a standardized method [13]. The ultrasound examination was done in mode B, on a longitudinal section, at the level of both common (CCA) and internal (ICA) carotid arteries,

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bilaterally. The IMT measurement was performed at the distal wall of the CCA and ICA, at 10 mm of the bifurcation, in the area without any atheroma plaque. The value used for the subsequent statistical analysis was the average of the three measurements on each side. Medium IMT values greater than 1 mm were considered to be elevated. No values greater than or equal to 1.5 mm were taken into account (these representing the formation of the atherosclerotic plaque). All measurements were performed by the same examiner to eliminate possible differences.

We also measured weight and height, and collected blood to determine total cholesterol and triglycerides levels. All of these parameters were obtained by standardized methods [14]. Based on the anthropometric parameters, the body mass index (BMI) was calculated according to the formula: $G(kg)/T^2(m^2)$. BMI is the most used surrogate parameter to estimate excess weight. For the lipid profile, we considered values above 200mg/dL as increased for total cholesterol and above 150 mg/dL for triglycerides.

Statistical analysis was performed with SPSS v.18. In interpreting statistical results we considered $p=0.005$ as the reference value for significance, which corresponds to a confidence interval of 95%. Continuous type variables were presented as mean ± standard deviation.

Results and discussions

Among a total of 176 subjects (106 women, 70 men), 47 were in the stroke group, 48 were first degree relatives and 81 were healthy controls. In the control group, the mean age was 54.53±15.6 years, with 64.5% females, the mean BMI was 26.8±5.02 kg/m^2, the mean value of cholesterol was 181.4±40.1 mg/dL and the mean value of triglycerides was 108.7±62.3 mg/dL. In the group of stroke patients the mean age was 52.7±15.07 years, with 46.8% females, the average BMI was 26.5±5.3 kg/m^2 and the mean cholesterol and triglycerides were in the normal range (165.3±43.9 mg/dL,134.1±42.9mg/dL respectively). The relatives of the stroke patients were 58.3% women; 56.3% had the mother with stroke, 39.6% had the father with cerebrovascular disease and 4.2% had both parents with ischemic stroke. This group had a mean BMI of 28.3±5.2 kg/m^2 and the mean cholesterol and triglyceride levels were within the normal range (142.6±40.1 mg/dL, 106.9±27.7 mg/dL). The statistics for the entire study population is presented in the table below (table 1).

The core discussion in assessing risk for stroke is the way modifiable risk factors could be improved, especially cholesterol and triglycerides values [15]. In our study, only 12.8% of stroke patients had increased cholesterol levels, but statistically insignificant compared to the other groups. This contradicts data in the literature [16]. Furthermore, the mean cholesterol in stroke patients was 165.3±43.9 mg/dl, whether or not the patient was undergoing hypolipidemic therapy. There were no statistical significant differences in the values of cholesterol between the three groups, nore in the percentage of subjects with increased cholesterol, between the groups.

Another lipid parameter considered was the triglycerides level. In patients with stroke, hypertriglyceridemia was found in 27.7% of patients, which was statistically insignificant compared to the other groups. The average value of triglycerides in stroke patients was 134.1±42.9 mg/dL regardless of whether or not patients were on the medication to lower triglycerides. This was also in contradiction with data in the literature [17]. Furthermore, only 6.3% of first degree relatives of stroke patients had hypertriglyceridemia, with an average of 106.9±27.7 mg/dL, which does not motivate the introduction of a hypolipidemic medication to prevent stroke. In the control population, the mean value of triglycerides was also in the normal interval. We found a statistically significant difference between the triglyceride value in healthy controls and the value of the first-degree relatives of stroke patients ($p=0.002$) (table 2).

Studies have shown that the value of triglycerides is directly proportional to the average IMT and thus the risk of developing stroke. In our study, we found a statistically significant correlation between the triglycerides value and the IMT measured at the right CCA ($p<0.001$) or left CCA ($p=0.025$) in stroke patients (fig. 1).

We also found a statistically significant difference between the triglyceride levels in relatives and mean IMT measured at the left ICA in patients with stroke ($p<0.001$). Our results once again advocate the recommendations of the current stroke guidelines of 2018 about the usefulness

		Age (years)	BMI (kg/m^2)	Cholesterol (mg/dl)	Triglycerides (mg/dl)
Mean		50.4830	27.1795	166.5511	115.0568
Median		51.0000	26.5000	159.0000	101.0000
Std. Deviation		15.73203	5.19955	43.99971	51.02243
Minimum		21.00	17.00	90.00	39.00
Maximum		82.00	51.00	310.00	510.00
Percentiles	25	36.0000	24.0000	138.0000	88.2500
	50	51.0000	26.5000	159.0000	101.0000
	75	63.0000	30.0000	190.2500	123.0000

Table 1
MEAN VALUES FOR THE STUDY POPULATION

	Stroke	Relatives	Control patients
Hypercholesterolemia (%)	12.8	6.3	16
Cholesterol - mean value±SD (mg/dl)	165.3±43.9	142.6±40.1	181.4±40.1
Hypertriglyceridemia (%)	27.7	6.3	16
Triglycerides - mean value±SD (mg/dl)	134.1±42.9	106.9±27.7	108.7±62.3

Table 2
CHOLESTEROL AND TRIGLYCERIDES IN THE STUDY GROUPS

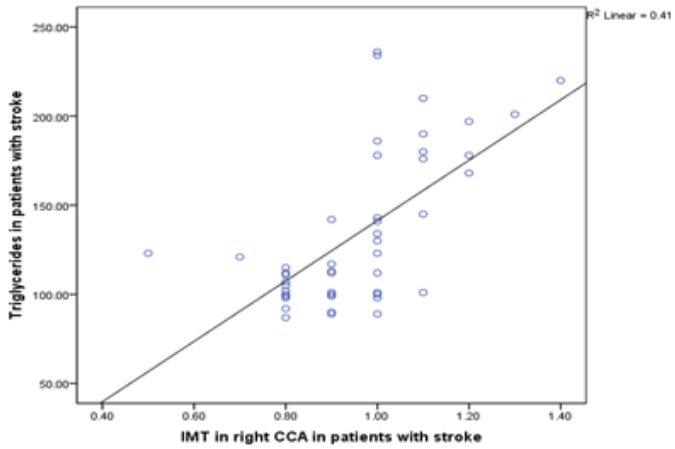

Fig. 1. Correlations between the IMT in the right CCA in patients with stroke and values of triglycerides

of lipid-lowering medication in preventing the development of atherosclerotic plaque (fig. 2).

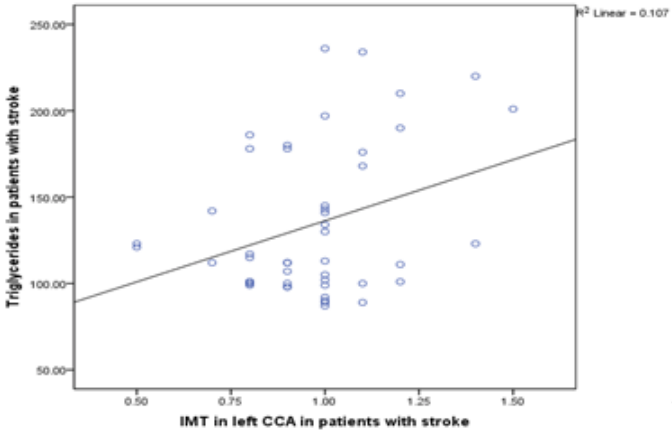

Fig 2. Correlation between triglycerides and IMT in the left CCA in stroke patients

We also found a statistically significant difference between the triglyceride value in the control group and the mean IMT measured at the left CCA in stroke patients ($p=0.028$). So, not only the triglyceride value influences the incidence of stroke, but it appears that other factors stimulate the appearance and thickness of the atheroma plaque (fig. 3).

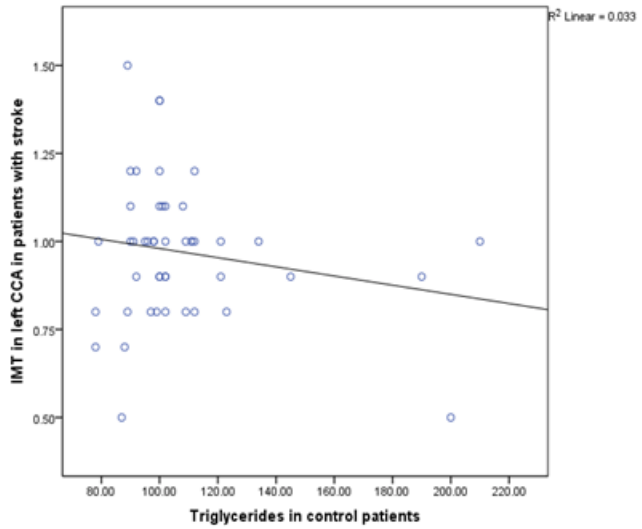

Fig 3. Correlation between triglycerides in control patients and IMT in left CCA in stroke patients

The involvement of genetics in the development of the atherosclerotic plaques in patients with stroke is again proven. Thus, in our study, we found a statistically significant difference between the mean IMT measured at the right ICA in first-degree relatives with the IMT measured at the left CCA in patients with stroke ($p=0.01$) (fig. 4).

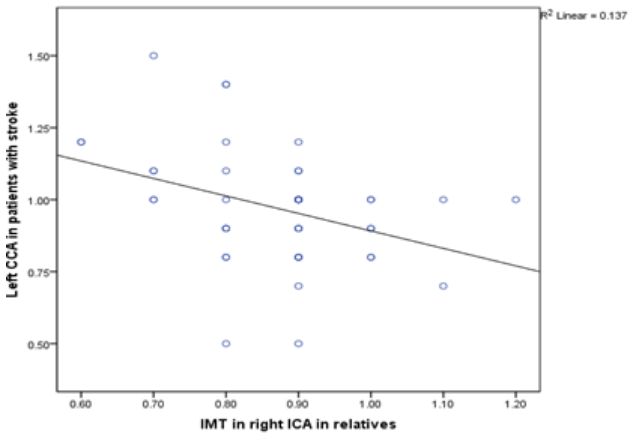

Fig 4. Correlations between IMT in left CCA in stroke patients and in right ICA in their relatives

The predisposition of patients to develop stroke through generalized atherosclerosis is confirmed in our study. Thus, we found a statistically significant difference between IMT measured at the left and right CCA in patients with stroke ($p<0.001$) (fig. 5).

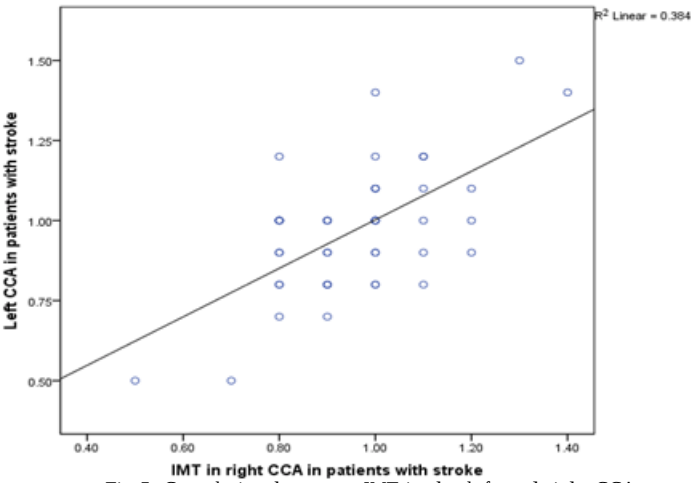

Fig 5. Correlation between IMT in the left and right CCA in stroke patients

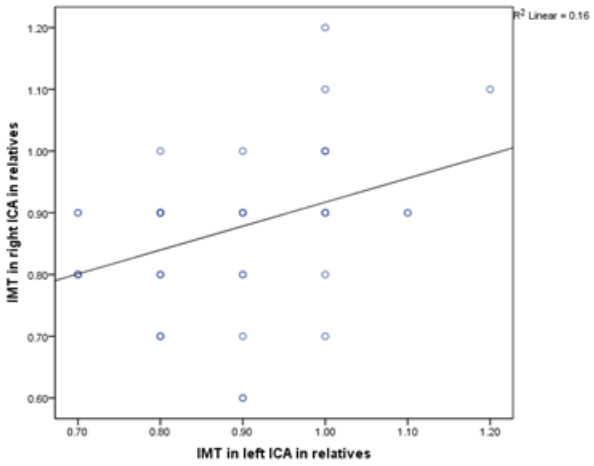

Fig 6. Values of IMT in right and left ICA in stroke patients relatives

To confirm the above, the average IMT is modified not only in patients with stroke but also in their first degree relatives (mainly the patients' children). Thus, in our study we found a significant difference between the thickness of the intima media measured at the right and the left ICA in the first degree relatives of stroke patients ($p=0.005$) (fig. 6).

Conclusions

Stroke is one of the most common pathologies, with a great disabling potential, but is at the same time one of the neurological diseases well suited for primary and secondary prevention. Carotid IMT is one of the best markers for atherosclerosis, but in the same time an independent risk factor for the atherosclerosis process, which is the central phenomenon encountered in the etiology of ischemic stroke. In our study, we noticed the involvement of genetic factors in the occurrence of subclinical atherosclerosis in stroke patients. We also noticed the involvement of the genetic factor in the occurrence of subclinical atherosclerosis in the first-degree relatives of stroke patients and therefore the need for lipid-lowering medication to prevent stroke in these individuals. The involvement of triglycerides in the atherosclerosis process has been objectively reflected in our study in patients with stroke and their relatives. After statistical data processing, we found no relationship between cholesterol levels and changes in subclinical atherosclerosis in patients with stroke and their relatives.

Stroke is characterized by an increasing prevalence linked to the presence of a substantial number of modifiable risk factors, a high rate of long-term disability, as well as direct and indirect costs at national and international level. Because of these reasons, our study can help develop a screening algorithm for the primary prevention of stroke in first-degree relatives of stroke patients.

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