

## Correlations between etiological factors and lesion severity in carotid artery atheromatosis

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### Abstract

Occurrence of atheromatous plaques on the internal wall of large and medium sized arteries represents a widely spread disease. It is especially found in the elderly, but also in individuals belonging to the 4<sup>th</sup>–6<sup>th</sup> decade of life with an increasing incidence. Correlating the main etiological factors with morphological change severity, in conjunction with settling the importance of each factor on its own in generating and developing arterial plaques, has an important predictive role in the evolution of atherosclerotic pathology. The purpose of this study is to investigate the existence of a correlation between the main factors linked to atheromatosis and the degree of severity of the carotid artery stenosis. This is obtained by ultrasonographic examination of the carotid arteries in correlation with determining serum cholesterol levels, thus ascertaining the risk for atheroma related events and disease progression.

**Keywords:** atheroma, ultrasonography, cholesterol, diabetes, smoking.

### Introduction

Occurrence of atheromatous plaques on the internal wall of large and medium sized arteries represents a widely spread disease. It is especially found in the elderly, but also in individuals belonging in the 4<sup>th</sup>–6<sup>th</sup> decade of life with an increasing incidence.

More than 50% of deaths worldwide are related to ischemic events in the vascular territory irrigated by the carotid artery. Cerebral stroke represents the third most frequent cause of death at a global level.

Considering the fact that a large amount of cases presenting with vascular related cerebral events are followed by motor or sensory-motor deficits of various degrees, and the fact that those patients will be unable to work, some of them requiring round the clock care, thus social dependence, we can deduce the real importance of this vascular pathology [1, 2].

Until three decades ago, vascular exploration was realized mostly aided by invasive techniques, arteriography being the standard procedure. As science progressed, a large array of less invasive techniques arose concerning vascular imaging, with widespread implementation. Thus, ultrasonography, computed tomography (CT) and magnetic resonance imaging (MRI) started constituting a correct alternative for angiographic studies.

In spite of the fact that non-invasive procedures can offer important data in relation to vessel diameter, structure and hemodynamics, arteriography holds its place amongst diagnostic procedures. Moreover, arteriography has a significant importance as a minimally invasive therapeutic tool, results getting better and better as experience and technique progress.

Amongst the non-invasive methods for investigating

large and medium sized arteries, ultrasonography is by far the most used, being not only the most accessible for both the patient and examiner alike, but also having high degrees of sensitivity and specificity referring to arterial disease.

Currently, ultrasonographic investigation represents the standard of care in examining and monitoring patients with vascular related neurological disease. It is an inexpensive, accessible and non-invasive option, easily tolerated by the patient, while offering important diagnostic data from before and after a therapeutic maneuver. From a statistical standpoint, echography has both sensitivity and specificity more than 90%, only low-grade stenoses with no significant hemodynamic change have predictive measures less than 90% [3].

Correlating the main etiological factors with morphological change severity, in conjunction with settling the importance of each factor on its own in generating and developing arterial plaques, has an important predictive role in the evolution of atherosclerotic pathology.

The present study aims to investigate the correlation between the main etiological factors linked to carotid atheromatosis and the arteries' morphological degree of lesion severity, more specifically to present the link between the degree of luminal stenosis in the carotid arteries measured ultrasonographically and the predictive power of determining serum level of cholesterol, thus establishing future risk for occurrence and progression of arterial atheromatosis.

### Patients, Materials and Methods

The study has been developed on a group of 270 patients. The ultrasonographic studies have been performed with the following devices: ALOKA 4000, E-CUBE 9 and

VOLUSUN 8, with linear transducers of 7.5 up to 9 MHz. Each patient underwent B mode, color Doppler and power Doppler of the common carotid artery, carotid bifurcation and internal carotid artery bilaterally, using longitudinal and transversal sections through each artery.

In monitoring the serum cholesterol level, we organized our data on the classification developed by the *United States Department of Health and Human Services*, according to Table 1 [4].

**Table 1 – Classification of the serum cholesterol level**

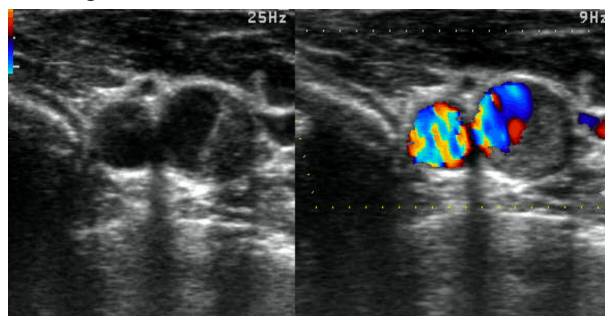
<200 mg%	Normal
200–239 mg%	Borderline
>240 mg%	High

In evaluating the carotid artery permeability and relative risk for producing cerebral vascular events, we classified the degrees of stenosis as follows:

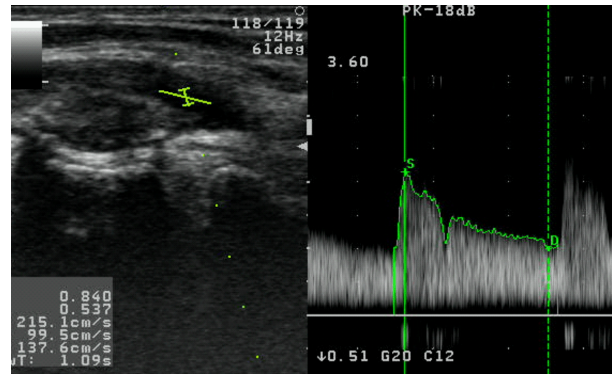
- I<sup>st</sup> degree: 0–75% – lack of carotid blood flow modifications, stenoses being named hemodynamically insignificant stenoses;
- II<sup>nd</sup> degree: 75–90% – carotid arterial flow moderately modified (turbulent flow with increase in velocity and lower flux), being named hemodynamically significant stenoses;
- III<sup>rd</sup> degree: 91–99% – carotid arterial flow severely modified (turbulent flow with high increase in velocity and lower flux), being named hemodynamically critical stenoses;
- IV<sup>th</sup> degree: 100% – absence of flow; in the ultrasonographic examination, we will refer to the lack of blood flow as occlusion.

From an ultrasonographic standpoint, a classification of types of atheromatous plaques belongs to Gray–Weale *et al.* [5], which will be also used in our study as follows:

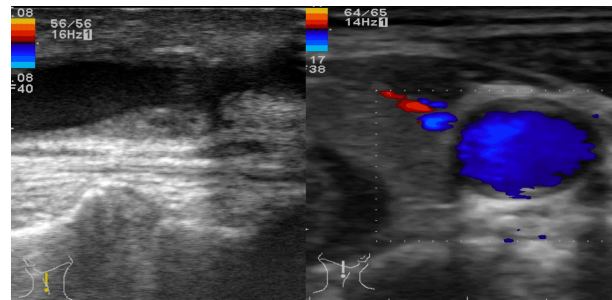
- Type I plaque – hypoechogenic, homogeneous, sometimes hard to observe in 2D mode examination. It presents a fine surface, with no irregularities. Sometimes power Doppler can aid in the visualization of an intraluminal area with no blood flow, as shown in Figure 1;
- Type II plaque – non-homogeneous structure, predominantly hyperechogenic (more than 75%), presenting small areas of hyperechogenicity (less than 25%). It has a clear margin that is hard to visualize or it is associated with an inexistent internal vascularization in power Doppler Mode, aspect presented in Figure 2;
- Type III plaque – hyperechogenic plaque (up to 75% of volume), presenting hypoechogenic areas inside the plaque (up to 25%), uneven contours, as in Figure 3;
- Type IV plaque – completely hyperechogenic plaque with or without micronodular calcifications, uneven contour, as in Figure 4.



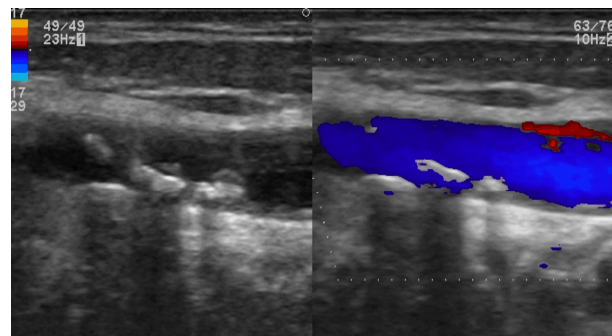
**Figure 1 – Type I plaque: ultrasonographic transverse B-mode and pulsed Doppler aspects.**



**Figure 2 – Type II plaque: ultrasonographic aspect.**



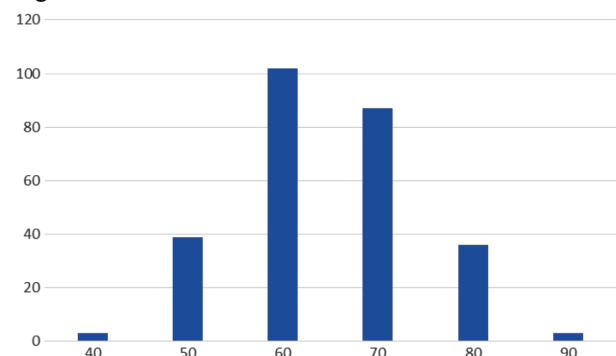
**Figure 3 – Type III plaque: ultrasonographic aspect.**



**Figure 4 – Type IV plaque: ultrasonographic aspect.**

## Results

The study was conducted on a group of 270 patients, with ages between 39 and 81 years old. The gender distribution of the group was represented by 168 males and 102 females. The age group distribution is presented in Figure 5.



**Figure 5 – Age distribution of patients on age groups.**

Patients have been asked about their smoking habits before proceeding to perform the ultrasonographic examination. We classified as smokers patients that smoke more

or equal to 10 cigarettes per day or have been smoking for the past 20 years or have quit smoking no later than five years. The group distribution in accordance with smoking habit can be found in Figure 6.

Another variable monitored by our study was the presence of diabetes mellitus. Out of the 270 patients enrolled in the study, 81 presented diabetes, requiring oral medication or being insulin-dependent. Their distribution can be observed in Figure 7.

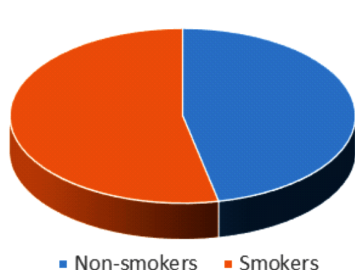


Figure 6 – Group distribution in accordance with smoking habits.

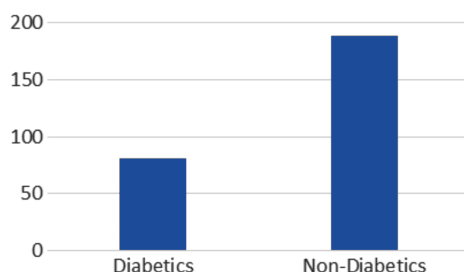


Figure 7 – Group distribution in accordance with the presence of diabetes.

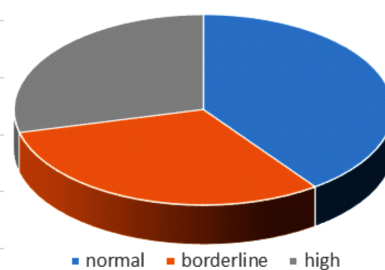


Figure 8 – Group distribution in accordance with serum cholesterol values.

### Atheroma plaques

Atheroma plaques detectable by ultrasonography have been registered along with their position and degree of stenosis. Accordingly to the classification devised by our research group, the patients were split into four groups, as presented in Figure 9: 228 patients presented insignificant stenosis, one patient presented with significant stenosis, 14 patients presented with critical stenosis, while 27 patients presented with carotid artery occlusion unilaterally (26) or bilaterally (one patient).

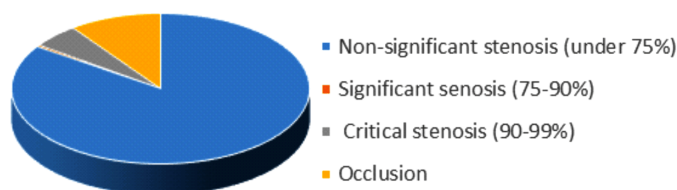


Figure 9 – Percentage distribution of the group by degree of stenosis.

In addition to echographic examination of the carotid arteries, we also monitored the level of total serum cholesterol. Normal, borderline and high values were noted in accordance with the *United States Department of Health*.

Out of the entire group, only 78 patients presented with a high blood cholesterol level, the evaluation of the rest of the patients indicating normal or borderline values. The distribution can be observed in Figure 8.

Referring to the position, number and distribution of the carotid plaques, the patients have been distributed into three groups as follows:

- 26 patients presented with unilateral carotid stenosis;
- 25 patients from the investigated group did not present with any atheroma plaques;
- the rest of 219 patients presented bilateral carotid plaques, with different degrees of stenosis, as can be observed in Figure 10.

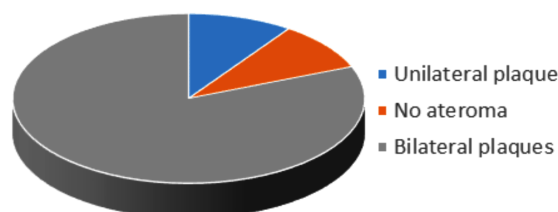


Figure 10 – Group distribution according to plaque position.

In order to process our data from a statistical point of view, we implemented a multinomial logistic regression model, the stenosis representing the dependent variable (the effect), while the occlusion represents the report base.

The 270 observations (patients) have been divided into 12 subpopulations depending on the possible combinations between the studied variables, such as diabetes, smoking and cholesterol. In five of these subpopulations, representing 41.9% of the studied group, there are recorded values corresponding to the same predisposition for a certain type of stenosis.

The analyzed model is valid for a significance threshold of 1% (99% probability of guaranteeing the results). In other words, at least one of the inquired variables (diabetes, smoking or serum cholesterol level) are significant (values of the B coefficient differ from 0) (Table 2).

After testing parameter signification, we can observe that:

1. For the case of insignificant stenosis compared to carotid artery occlusion:

(a) Patients that do not suffer from diabetes are 5.034

less likely to develop a carotid artery occlusion than an insignificant stenosis, compared to diabetics. This conclusion is valid with a probability of 98.7%.

(b) Non-smokers are 64.3% more likely than smokers to develop an insignificant stenosis, in comparison to carotid occlusion. The conclusion is valid with a 97.2% degree of confidence.

(c) Patients with a normal blood cholesterol level are 9.83 times more prone to present with an insignificant stenosis compared to an occlusion, when compared to the group of patients with hypercholesterolemia.

2. In the case of comparison between patients with significant stenoses and arterial occlusion: in this case, there is only one significant factor, which is diabetes. Patients that do not suffer from diabetes are with 64.6% more prone than diabetics to present with a significant stenosis rather than an occlusion. The degree of confidence is 92.9%.

3. For the comparison of the patients presenting with critical stenoses with the patients with carotid artery occlusions, no factor influences the probability for developing a carotid artery occlusion in the future.

We applied a model of polynomial logistic regression, stenosis being the dependent variable (the effect), and the carotid artery occlusion being considered the baseline.

For the group of non-diabetic non-smoker individuals in this study, the cholesterol level does not influence the probability of developing a non-significant stenosis compared to a carotid artery occlusion, or none of the serum cholesterol levels do not represent a significant factor (the coefficients are equal to 0).

For the group of non-diabetic smokers, individuals with a normal serum cholesterol level are 2.824 more likely than those with a high serum cholesterol level to develop a non-significant stenosis rather than a carotid artery occlusion, with a degree of trust of 82%.

In diabetic non-smoker patients, the serum cholesterol level does not influence the probability of developing insignificant carotid stenosis compared to the odds of developing carotid artery occlusion (the coefficients are equal to 0).

For the case of diabetic smoker patients, the serum cholesterol level does not influence the probability of developing a non-significant stenosis in comparison to a carotid artery occlusion (coefficients are equal to 0).

#### Cholesterol-related stenosis taking smoking as a variable

For non-smokers, the serum cholesterol level does not influence the eventuality of developing any type of stenosis (insignificant, significant, critical) in comparison

to artery occlusion, none of the cholesterol level classes used in this study representing a significant factor (coefficients are 0).

For smokers with a normal cholesterolemia, there is a 3.556 times greater chance to develop I<sup>st</sup> degree stenosis rather than a IV<sup>th</sup> degree stenosis when taken in comparison with the smokers with modified cholesterol levels. The degree of confidence is 92.4%.

For smokers, cholesterol serum levels do not make a difference between the risk of developing II<sup>nd</sup> degree stenosis and IV<sup>th</sup> degree stenosis, thus normal, borderline and high cholesterol levels are not significant factors (coefficients are 0) (Table 3).

#### Stenosis in relation with cholesterol serum levels for diabetes as a variable

For non-diabetics with normal serum cholesterol level, there is a 7.2337 times more likely chance to develop I<sup>st</sup> degree stenosis than IV<sup>th</sup> degree stenosis when compared to the group of diabetics with hypercholesterolemia. The degree of confidence is 99.7% (Table 3).

#### Atheroma progression considering cholesterol as a variable

From our data, we can infer with a degree of confidence of 88% that an individual with a borderline serum cholesterol level has a 57.3% lower predisposition towards bilateral atheromatous plaques compared to an individual with hypercholesterolemia.

Table 2 – Estimation of parameters

	Independent variables	B (variable coefficient)	Significance	Exp (B)
<b>Patients with non-significant stenoses</b>	Intercept (free term)	-4.190	0.000	
	Non-diabetic	1.616	<b>0.013</b>	<b>5.034</b>
	Non-smoker	-1.031	<b>0.028</b>	<b>0.537</b>
	Normal cholesterol	2.285	<b>0.010</b>	<b>9.830</b>
	Borderline cholesterol	0.376	0.607	1.457
<b>Patients with significant stenoses</b>	Intercept (free term)	-2.205	0.002	
	Non-diabetic	-1.033	<b>0.071</b>	<b>0.356</b>
	Non-smoker	-0.536	0.372	0.585
	Normal cholesterol	0.455	0.557	1.576
	Borderline cholesterol =2	0.193	0.794	1.213
<b>Patients with critical stenoses</b>	Intercept (free term)	-38.276	0.997	
	Non-diabetic	-18.559	0.998	0.00000087
	Non-smoker	17.396	0.998	35 907 026.513
	Normal cholesterol	18.079	0.998	71 079 136.965
	Borderline cholesterol	0.317		

Table 3 – Cholesterol level dependent degrees of carotid artery stenosis for different combinations, with smoking and diabetes as independent variables

			Observations	Percent
<b>Non-diabetic</b>	<b>Non-smoker</b>	Patients with non-significant stenoses	9	10%
		Carotid artery occlusion	<b>81</b>	<b>90%</b>
		Patients with non-significant stenoses	30	33.3%
		Borderline cholesterol	29	32.2%
		High cholesterol	<b>31</b>	<b>34.4%</b>
<b>Diabetes</b>	<b>Smoker</b>	Patients with non-significant stenoses	15	15.2%
		Patients with significant stenoses	78	78.8%
		Carotid artery occlusion	<b>6</b>	<b>6.1%</b>
		Patients with non-significant stenoses	23	23.2%
		Borderline cholesterol	46	46.5%
		High cholesterol	<b>30</b>	<b>30.3%</b>

		Observations	Percent	
<b>Diabetes</b>	<b>Non-smoker</b>	<b>Carotid artery occlusion</b>	<b>30</b>	<b>83.3%</b>
Thirty-six observations grouped in three subpopulations according to cholesterol and stenosis criteria		Patients with significant stenoses	5	13.9%
		Patients with critical stenoses	1	2.8%
		Patients with non-significant stenoses	20	55.6%
		Borderline cholesterol	8	22.2%
		<b>High cholesterol</b>	<b>8</b>	<b>22.2%</b>
<b>Diabetes</b>	<b>Smoker</b>	Patients with non-significant stenoses	3	6.7%
Forty-five observations grouped in three subpopulations according to cholesterol and stenosis criteria		<b>Carotid artery occlusion</b>	<b>39</b>	<b>86.7%</b>
		Patients with significant stenoses	3	6.7%
		Patients with non-significant stenoses	13	28.9%
		Borderline cholesterol	24	53.3%
		<b>High cholesterol</b>	<b>8</b>	<b>17.8%</b>

## Discussion

Atheromatosis represents the main cause for cerebral ischemic events, having various consequences in the patients' lives, ranging from absence of neurological deficit to persistent severe loss of motor function and sensation. Some cerebral strokes end up being lethal.

Ultrasonography gained an important role in the non-invasive examination of the carotid and vertebral arteries, not only as a diagnostic tool but also as a mean to predict future development of a possible cerebrovascular event.

The main cause of stroke is constituted by plaque formation and progression in the intimal layer, leading to either stenosis or vessel occlusion. Another well-documented mechanism for stroke is the fragmentation of the plaque, thus generating emboli that migrate upstream in the cerebral arterial system.

The elective position for initiation and progression of atheroma plaques is located at the vascular bifurcations.

From the statistical data gathered and interpreted in our centre, we were able to draw a battery of conclusions, some in accordance with international specialty literature, some poorly correlated as follows:

In our daily practice, we discovered that serum cholesterol levels alone cannot be predictive for the presence and the degree of severity in carotid arterial disease. In accordance, we started monitoring a possible correlation between total cholesterol level and the number, volume and degree of atheroma plaques, and not lastly the degree of carotid stenosis.

In a significant amount of cases, patients with hypercholesterolemia not presenting with other predisposing factors (smoking, diabetes) do not have hemodynamically significant stenoses determined by atheroma plaques. In addition, other patients with normal serum cholesterol levels, but having other associated risk factors such as smoking or diabetes or both, with hemodynamically significant stenotic lesions.

In this research direction, several studies found that there is a high prevalence of atheromatous disease in type 2 diabetes patients, with a risk of stenosis occurrence in male patients associating coronary disease, in more than 60% of cases [6–8]; other papers state that diabetic patients are three times more predisposed to develop carotid artery stenosis in comparison to non-diabetic patients [9].

Smoking has been strongly linked to arterial wall

thickening in the carotids [10]; however, other studies prove that not all carotid artery stenoses can be directly attributed to smoking, it being an independent determining factor in patients with carotid artery occlusion and cerebral ischemia [11].

Other studies state that age and smoking are independent determining factors linked to carotid artery atheromatosis severity [12, 13].

Regarding serum cholesterol levels as a risk factor for carotid atheromatosis, some studies mention hypercholesterolemia as an independent risk factor in carotid stenosis [7]. From data gathered in this study we can state that subjects with high levels of serum cholesterol and no other predisposing factors associated, did not present with hemodynamically significant stenoses; on this matter, some studies mention that there is not yet clear what is the cholesterol's role in the formation of atheromatous plaques and its link to the stenosis degree. That can be partially explained by contradictory studies [14]. We ought to mention the fact that our study did not monitor and analyze the cholesterol fractions, ergo cannot appreciate the role of high-density lipoprotein (HDL)- and low-density lipoprotein (LDL)-cholesterol in atheromatous plaques' formation and progression. Another limitation of our study is that our data does not give us the possibility to ascertain the correlation between lowering cholesterol levels and ischemic heart disease, according to age [15].

## Conclusions

Determining serum cholesterol levels does not represent a sufficient test for appreciating the risk of developing medium and large vessel atheromatosis. Moreover, hypercholesterolemia, while not being associated with other predisposing factors, does not involve increased risk for atheromatosis. From a more complex standpoint, associating hypercholesterolemia with diabetes or smoking or both significantly increases the risk of developing atheromatosis, whereas smoking and diabetes are high risk factors for the development of atheromatosis, even if associated with normal serum cholesterol levels. In addition, borderline serum cholesterol levels associated with high blood glucose, smoking or both, increases the predisposition for atheroma related carotid stenosis.

## Conflict of interests

The authors declare that they have no conflict of interests.

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