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Article

Vascular Risk Factors and Carotid Atheromatous Disease in Patients over 65 Years of Age

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Abstract: Introduction: Vascular risk factors are decisive in atherosclerotic disease evolution and the carotid and vertebral Doppler ultrasound allows monitoring its onset and progress. The measurement of arterial wall thickening allows the early diagnosis of the disease enhancing its treatment and control of vascular risk factors. **Aim:** To analyse the presence of atheromatous disease in individuals aged > 65 years and understands its correlation with vascular risk factors. **Materials and Methods:** Cross-sectional observational study, in individuals aged > 65 years who underwent carotid echoDoppler between january 1, 2012 and december 31, 2021. The intimal-media index was calculated, as was the presence of atheromatous plaques, their hemodynamic repercussion and vascular risk factors were recorded. **Results:** A sample of 5885 individuals was obtained with 41.8% female and 58.2% male. The mean age was 76.59, with a range between 65 and 98 years (+6.69). Arterial hypertension was the most prevalent 81.3%. There was a significant positive relationship between intima-media index, age and personal history of cardio and cerebrovascular diseases (p=0.001). In the presence of plaques, male gender, arterial hypertension, diabetes, dyslipidemia, smoking and personal history of cardio and cerebrovascular diseases present a positive correlation. **Conclusions:** In this sample, non-modifiable vascular risk factors seem to be determinant in the presence of increased arterial wall thickness. In the presence of signs of a more advanced stage of atherosclerotic disease, modifiable vascular risk factors are decisive, corroborating the already known importance of strict control of these for their treatment.

Keywords: Carotid atherosclerosis; cardiovascular risk factors; carotid intima-media thickness

Introduction

Vascular risk factors that contribute to atherosclerotic disease can be non-modifiable such as age, ethnicity, gender and family history of atherosclerosis, or modifiable risk factors, which can be controlled through re-education for healthy lifestyles, such as arterial hypertension, diabetes mellitus (DM), hypercholesterolemia, hypertriglyceremia, obesity, smoking, sedentary lifestyle, excessive alcohol consumption and embolic heart diseases (such as atrial fibrillation (AF), patent foramen ovale...) [1–5].

Atherosclerosis is an inflammation that occurs mainly in the arteries of medium and large calibre, in a chronic and progressive way, due to the progressive and/or sudden change in the composition of the blood, through the effect of risk factors, resulting in damage to the vessel wall. This inflammation will result in the increasing deposit of lipids, calcium, blood cells and constituents in the vessel walls, forming atheromatous plaques that, in more severe cases, affect blood circulation and lead to ischemia in the dependent territory [6,7].

Atherosclerosis is the etiology that can affect the coronary arteries, with a risk of angina pectoris and/or acute myocardial infarction, it also affects the arteries of the limbs resulting in peripheral vascular disease and affects extra and/or intracranial arteries, being a factor risk of ischemic stroke.[6,7] The highest occurrence of this type of pathology, as a rule, occurs in the elderly population over 65 years and in males. [4]

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Carotid arteries are among the vessels most affected by atherosclerotic disease due to their size and turbulence of flow at the bifurcation. That is why it is extremely important to have an early perception of the presence of atheromatous disease, which is characterized in an initial phase by lipid infiltration, later evolving into atheromatous plaques and reduction of the carotid lumen due to stenosis. This study is performed by cervical Doppler ultrasound of the carotid and vertebral arteries, allowing the quantification of arterial wall thickening called the intima-media index (IMI), which has great potential for the non-invasive assessment of atherosclerotic disease, as well as the presence of atheromatous disease in more advanced stages, already with the presence of atheromatous plaques and respective hemodynamic repercussions. Several studies point to a relationship between the incidence of cardio and cerebrovascular diseases and increased IMI values. This represents the earliest form of atheromatous disease, being a risk marker for acute myocardial infarction (AMI) and stroke, which justifies continued research and interest in this topic.[8–10] Cardio and cerebrovascular diseases of atheromatous origin are the main cause of mortality and morbidity in Portugal, namely in the Alentejo region. This is a particular region because of its own gastronomic and demographic characteristics, namely with high fat level and a very aged population.[3,11,12] We consider the over 65 years old as the elderly cut-off in Portugal.[11] With that premise we designed this study aiming to analyse the presence of atheromatous disease in a group of individuals aged more than 65 years-old from Alentejo region, and understanding its correlation with vascular risk factors.

Material and methods

The non-probabilistic sample for convenience consisted of 5885 individuals aged 65 years or older who underwent the cervical Doppler ultrasound examination at Hospital between January 2002 and December 2021 and about which it was possible to collect information on cardiovascular risk factors, as well as Doppler ultrasound findings on the carotid and vertebral arteries and corresponding IMI values. The variables collected for the study were gender, age, race, personal and family history of AMI and stroke, presence of hypertension, smoking habits, presence of dyslipidemia, AF, presence of other embolic heart diseases, presence of diabetes mellitus IMI and Doppler ultrasound results of the carotid axes (right and left) and vertebral arteries, Qualitative variables (arterial hypertension, family and personal history of stroke and AMI, dyslipidemia, AF, DM and other embolic heart diseases) were subdivided into "yes" which corresponds to the presence of co-mobility in the individual and "no" to its absence. The qualitative variable gender was characterized by "male" and "female", race by "black" and "Caucasian", and in the variable smoking, the description "ex-smoker" was added, which included cases that quit smoking minimum of 12 months before the exam. In the variable other cardioembolic heart diseases (sinus node diseases, valvulopathies, endocarditis, presence of prosthetic valves, cardiomyopathies, congenital heart diseases and iatrogenic causes) the main potentially embolic heart diseases except AF were included as "yes". The data corresponding to the cervical Doppler ultrasound findings were grouped into carotid axes (includes mean value of left and right axis results) and vertebral arteries (includes mean value of left vertebral artery and right vertebral artery results) and were categorized into: normal exams, mild stenosis (<50%) and moderate stenosis (50%-69%), significant stenosis (70%-89%) and pre-occlusive stenosis (90%-99%), occlusions, atheromatous changes without hemodynamic repercussions, occlusions and others (where tortuosity, hypoplasia, etc. were included). The quantitative variables age and IMI had their corresponding numerical values described, with the IMI presented in millimeters (mm) and classified as normal when the numerical value is ≤0.9mm, thickening when found between 1mm and 1.3mm and atheroma when the numerical value is ≥1.4mm [13,14].

To quantify the degree and severity of carotid stenosis, the "North American Symptomatic Carotid Endarterectomy Trial" (NASCET) classification was used [15,16].

Family history of stroke and AMI and ethnicity were only analysed descriptively, as there was not much variability.

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In order to guarantee confidentiality and anonymity of all data, they were coded sequentially and numerically, without any personal identification, respecting the ethical principles contained in the Declaration of Helsinki. [17]

The G*power Software (G*power 3.1, University of Düsseldorf, Düsseldorf, Germany) was used to analyse conditions with a sample of 5881 individuals: effect size f = 0.25, α error probability = 0.05 and power (1-β error probability) = 0.95.

An individual descriptive analysis of each variable was carried out. For continuous variables, mean and standard deviation were calculated; categorical variables were presented as a percentage. In order to test the normality were performed using the Kolmogorov-Smirnov and Shapiro-Wilk tests.

For the evaluation of dependency relationships, the test according to the nature of the variables was used, including the Chi-square test; ETA test and C-Pearson. P-values <0.05 were considered statistically significant.

Statistical analysis was performed using SPSS statistical data analysis software (Statistical Package for the Social Sciences, IBM SPSS Statistics®23) in the Windows 10® version.

Results

A total of 5885 individuals were evaluated, of which 41.8% were female and 58.2% were male, with a mean age of 76.59 years + 6.686 and a maximum of 98 years.

Risk factors

With regard to the remaining risk factors, given the existence of only one black individual, this factor was not subject to statistical analysis. Of note are 30.8% of individuals with a personal history of stroke and 7.2% with a personal history of ADE (Table 1).

As for modifiable risk factors, 81.3% of individuals had hypertension and 18.7% were normotensive. Dyslipidemia was present in 51.3% of individuals. With diabetes mellitus 31.4% and the vast majority of individuals did not report smoking habits (82.7%), 5.8% were smokers and 11.5% were ex-smokers. AF had a percentage of 16.6% and 3.6% with other cardioembolic heart diseases (Table 1).

Table 1. Frequencies and percentages of risk factors (n=5885).

Variable		Absolut frequencies	Percentage (%)
Personal history of stroke	No	4073	69,2%
	Yes	1812	30,8%
Personal history of AMI	No	5464	92,8%
	Yes	421	7,2%
Family history of stroke	No	5816	98,8%
	Yes	69	1,2%
Family history of AMI	No	5844	99,3%
	Yes	41	0,7%
Hypertension	No	1098	18,7%
	Yes	4787	81,3%
Dyslipidemia	No	2867	48,7%
	Yes	3018	51,3%
Diabetes *mellitus*	No	4036	68,6%
	Yes	1849	31,4%
Smoke habits	No	4864	82,7%
	Yes/ex-smoker	1021	17,3%

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AF	No	5025	85,4%
	Yes	860	14,6%
Other cardioembolic heart disease	No	5675	96,4%
	Yes	210	3,6%

Legend: AMI – acute myocardial infarction; AF – atrial fibrilation.

Exam results

The minimum value found for the IMI was 0.5mm and the maximum was 1.3mm with an average of 0.962mm (+0.170). About 46.6% of the individuals had increased IMI.

In the evaluation of the carotid axes by Doppler ultrasound, 13.6% of the exams were normal, 64.2% had atheromatous plaques, without hemodynamic repercussions; 6.1%atheromatous plaques conditioning moderate stenosis, in 5.4% atheromatous plaques conditioning significant pre-occlusive stenosis, and 3.3% with occlusion (by plaques, thrombus or atherothrombosis). The remainder (7.4%) had other alterations or variants of normality. Regarding the vertebral arteries, it was observed that most of the exams were normal (93.6%), 1.2% had atheromatous plaques, without hemodynamic repercussions, 0.3% atheromatous plaques with moderate stenosis, 0.3% atheromatous plaques conditioning significant stenosis to pre-occlusive, and 2.4% with occlusion. The remainder (2.2%) had other alterations or variants of normality (Table 2).

Table 2. Frequencies and percentages of cervical Doppler ultrasound results (n=5885).

Variables		**Absolut frequencies**	**Percentage (%)**
Carotid axes	Normal	803	13,6%
	Atheromatous plaques, without hemodynamic repercussions	3776	64,2%
	Moderate stenosis	359	6,1%
	Pre-occlusive stenosis	315	5,4%
	Occlusion	197	3,3%
	Other	435	7,4%
Vertebral axes	Normal	5507	93,6%
	Atheromatous plaques, without hemodynamic repercussions	36	1,2%
	Moderate stenosis	15	0,3%
	Pre-occlusive stenosis	14	0,3%
	Occlusion	139	2,4%
	Other	174	2,2%

In order to analyse the relationship of dependence between the various risk factors referred to and alterations in the carotid and vertebral axes, crosstabs and statistical tests were carried out and percentages were compared, in which significant correlations were verified between genders and the presence of increased IMI and atheromatous alterations in the Doppler ultrasound. at the level of the carotid and vertebral axes (p=0.000) there was a higher prevalence of IMI and alterations such as atheromatous plaques with or without stenosis in males compared to females. Regarding age, there is also a positive correlation with the IIM, which tends to have higher values with age. It should also be highlighted the presence of statistical significance between personal history of stroke and the presence of atheromatous disease, regardless of the stage or degree, and personal and family history

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of ADE in more advanced stages of atheromatous disease or other cervical arterial changes (Tables 3 and 4).

Table 3. Crosstabs between non-modifiable risk factors and modifiable risk factors with cervical ecoDoppler results (n=5885).

Variables			Cervical Doppler results		
			Normal (%)	Pathologic with hemodinamic repercurssion <70%	Pathologic with hemodinamic repercurssion ≥70%
Non-modifiable risk factors	Sex	female	6,9%	32,6%	2,3%
		male	5,8%	46,7%	5,7%
	Personal history of stroke	No	10,6%	54,2%	4,4%
		Yes	2,1%	25,1%	3,6%
	Personal history of AMI	No	12,1%	83,4%	7,3%
		Yes	0,5%	5,8%	0,9%
	Family history of stroke	No	12,6%	78,2%	8%
		Yes	0,2%	0,9%	0%
	Family history of AMI	No	12,6%	78,8%	7,9%
		Yes	0,1%	0,6%	0%
Modifiable risk factors	Hypertension	No	3,4%	13,9%	1,4%
		Yes	9,3%	65,3%	6,7%
	Dyslipidemia	No	6,9%	37,9%	3,9%
		Yes	5,7%	41,5%	4,1%
	Diabetes *mellitus*	No	9,5%	53,5%	5,6%
		Yes	3,2%	25,8%	2,4%
	Smoke habits	No	11,3%	65,1%	6,3%
		Yes/ex-smoker	1,3%	14,2%	1,8%
	AF	No	11,1%	67,3%	7%
		Yes	1,6%	12%	1%
	Other cardioembolic heart disease	No	12,4%	76,3%	7,7%
		Yes	0,3%	3%	0,3%

Table 4. Relationship between non-modifiable risk factors and cervical Doppler ultrasound results (n=5885).

Variable pairs		*p*-value
Non-modifiable risk factos	sex vs IMI	0,000
	sex vs carotid axes/vertebral axes	0,000/0,000

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	age vs IMI*	0.002
	age vs carotid axes/vertebral axes**	0.118/0.063
	personal history of stroke vs IMI	0,000
	personal history of stroke vs carotid axes/vertebral axes	0,000/0,000
	personal history of AMI vs IMI	0,327
	personal history of AMI vs carotid axes/vertebral axes	0,000/0,000
	family history of stroke vs IMI	0,895
	family history of stroke vs carotid axes/vertebral axes	0,083/1
	family history of AMI vs IMI	0,928
	family history of AMI vs carotid axes/vertebral axes	0,343/0,021

P-value calculation: Chi-square; * C-Pearson test; ** ETA.

With regard to modifiable risk factors, hypertension, DM and dyslipidemia stand out, which only showed statistical significance with the presence of alterations in the carotid axes and vertebral arteries, with hypertensive, diabetic or dyslipidemic patients being those who presented more changes. Smoking, on the other hand, showed a positive correlation with atheromatous disease in earlier stages (increased IMI) and in more advanced stages (presence of plaques with or without stenosis). AF had a significant correlation with the absence of atherosclerotic changes in the referred arteries (Tables 3 and 5).

Table 5. Relationship between modifiable risk factors and cervical Doppler ultrasound results (n=5885).

Variable pairs		***p*-value**
Modifiable risk factors	arterial hypertension vs IMI	0,183
	arterial hypertension vs carotid axes/vertebral axes	0,000/0,016
	DM vs IMI	0,316
	DM vs carotid axes/vertebral axes	0,000/0,039
	dyslipidemia vs IMI	0,418
	dyslipidemia vs carotid axes/vertebral axes	0,000/0,131
	smoke habits vs IMI	0,000
	smoke habits vs carotid axes/vertebral axes	0,000/0,000
	AF vs IMI	0,103
	AF vs carotid axes/vertebral axes	0,000/0,743
	other cardioembolic heart disease vs IMI	0,412
	other cardioembolic heart disease vs carotid axes/vertebral axes	0,745/0,270

P-value calculation: Chi-square.

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Discussion

The aim was to analyse the presence of atheromatous disease in a group of individuals aged 65 years or over in this hospital sample and to understand its correlation with vascular risk factors. It is described in the literature that advanced age is one of the most important risk factors for the development of atherosclerosis, constituting a public health problem due to the fact that in the more advanced age group (> 65 years) there is greater frailty, number of diseases and risk factors for atherosclerotic disease.

In this sample, there was a higher prevalence of males, as described in the results of other studies related to atheromatous disease and risk factors.[5,18] About 1/3 of the sample reveals a personal history of stroke/AMI. Data are in line with the literature.[6,7] According to some authors, atherosclerosis is the most frequent etiology and affects the coronary arteries, resulting in angina pectoris and/or acute myocardial infarction, affects the arteries of the limbs resulting in peripheral vascular disease and affects the extra and/or intracranial arteries, resulting in cerebrovascular accident (CVA).[6,7]

As for modifiable risk factors, it should be noted that most individuals are hypertensive (81.3%), about half of the sample have dyslipidemia (51.3%) and about 1/3 are diabetic. The average prevalence of hypertension found in the study is in line with what was expected and already reported in data from 2015, which refer to a prevalence of hypertension in the total Portuguese population of 36%, with a tendency to increase with advancing age.[19] Also the result of dyslipidemia and diabetes are in line with what is described in the consulted literature. In an epidemiological study by Mariano et al (2015), which refers to a prevalence of 52% of dyslipidemia in the Portuguese population.[20] According to Correia et al (2009) in Portugal, more than a quarter of the population has diabetes mellitus.[21] According to the guidelines of the Sociedade Brasileira de diabetes and the annual report of the national diabetes observatory in Portugal (2009), there is an increase in the prevalence of diabetes mellitus with the aging of individuals, thus concluding that the higher the average age, the greater the increase in the percentage of the disease.[21]

As for other factors such as AF and smoking, its low prevalence may be related to a higher frequency of smoking in younger age groups and with better financial conditions[22] and AF, despite being more prevalent in the elderly, is found to be higher after the age of 80 [23], diverging from our sample, which has a relatively lower average age, as well as the lack of knowledge on the part of patients about some co-mobilities.

With regard to Doppler echo findings, less than a quarter (13.6%) of the sample showed normal carotid arteries and almost all (93.6%) had normal vertebral arteries. This is in agreement with the literature, since the presence of pathology is more frequent in larger caliber vessels that are subject to more turbulent flows that condition intimal lesions, increasing the predisposition for the development of the atherosclerotic process. In this exam, the measurement of the carotid wall IIM value is an important parameter in the cerebrovascular area, since it is a predictor of atherosclerotic disease.[14] Naqvi et al. (2014) evaluated the intima-media index and atherosclerotic plaque in the assessment of cardiovascular risk and concluded that only the IIM value improves the predictive power of cardiovascular risk factors, but when the measurement is associated with the carotid bifurcation, it improves the prediction of disease atherosclerosis and stroke.[24] According to Blaha et al. (2014), if the objective is to calculate the risk of a stroke, the ultrasound image with measurement of the IMI must be used.[5] In this sample, about half (46.6%) presented an increased IMI, that is, it presents signs of the atherosclerotic process in the initial phase. More than half of the sample (64.2%) has atheromatous disease in the carotid axes, but without hemodynamic repercussions in most individuals, which is in line with the fact that atherosclerosis is a chronic pathology with slow evolution that worsens with increasing age.[25]

When analysing the relationship of dependence between the various risk factors referred to and changes in the carotid and vertebral axes, a significant relationship was observed between increased IMI and the presence of alterations such as atheromatous plaques with or without stenosis in males and in individuals with older ages, corroborating with previously mentioned studies. [5,17,25] A study carried out in 2008 reports that the IMI is associated with ages over 65 years.[25] In a meta-

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analysis carried out in 2017, it was concluded that the measurement of the thickness of the intima and media layers of the carotid arteries for assessment of cardiovascular risk, the IIM, increases with increasing age and male sex, due to the fact that with increasing age there is a greater development of multiple risk factors in the same individual that will cause to the increase of the IIM in relation to the younger ones.[9] In 2018, in a study with 84,880 individuals, a higher prevalence of carotid atherosclerosis was observed in males compared to the female and increased with age,[26] as well as in a previous study carried out in 1999.[17] Another study that evaluated the predictors of IMI and progression of atherosclerotic plaque in the Chinese population, found an association between increased IMI and progression of atherosclerotic plaque with gender, but a higher prevalence of these alterations was identified in females.[27] This and other studies point to a possible variability related to ethnicity and the region where the studies were carried out, since socioculturally there are customs where men play roles and have different habits (food, alcohol, sedentary lifestyle, education, profession and information on health).[27,28] In this sample the number of non-Caucasian individuals was small, thus these results are in agreement with the studies consulted with samples of similar characteristics.

The presence of statistical significance between the personal history of stroke and the presence of atheromatous disease, regardless of the disease stage (early or advanced), leads us back to the fact that IIM is associated with ages over 65 years and that atherosclerosis is a chronic pathology.[25]

With regard to modifiable risk factors, hypertensive, diabetic or dyslipidemic individuals showed statistical significance with the presence of changes in the carotid axes and vertebral arteries (more advanced stages of the disease). The findings of this study are in line with a study carried out in 2010, where the development of atheroma plaques in diabetic and hypertensive patients was evaluated, which showed that associations between the formation of atheroma plaques and HTA are observed in the literature.[29] In a study Chinese epidemiological study carried out in 2018, individuals were evaluated ultrasonographically for carotid atherosclerosis, showing a significantly high rate of hypertension.[26] The more advanced age groups are more prone to the presence of modifiable risk factors such as hypertension, which constitutes a one of the main risk factors for atherosclerotic disease, and it is expected that its presence, particularly in more advanced age groups, will influence the presence of atheromatous disease in medium and large caliber vessels, namely in areas of bifurcations or tortuosities that are very likely to damage the artery arterial wall and form atheromatous plaques.[30] Some studies have shown There are somewhat divergent results with regard to the relationship between hypertension and the different stages of the disease. In a study based on the evaluation of carotid atherosclerosis by echo-Doppler and the association with cardiovascular risk factors, AHT was not associated with carotid atherosclerosis, but with carotid intima-media thickening.[25] However, given the lower value (63 years) of the mean age of the sample in the study carried out may justify the absence of a positive relationship with more advanced stages of the disease and only being positive with the earlier stage.

As for dyslipidemia and diabetes, studies show that individuals with dyslipidemia have a higher prevalence of carotid atherosclerosis.[28] A meta-analysis revealed that they found 10 articles in which patients with dyslipidemia have a higher risk of developing carotid plaque and seven articles point to the fact of diabetic patients have a higher prevalence of atherosclerotic plaque than non-diabetic patients.[30] As previously mentioned, just like hypertension, diabetes mellitus is associated with atherosclerotic plaques. However, another study did not find statistical evidence of the association between carotid atherosclerosis and diabetes mellitus.[25] The literature presents inconsistent results on the subject.[29] The disagreement between studies is justifiable since it is described that diabetes mellitus is a risk factor for the development of atherosclerosis, mainly atherosclerosis of the microcirculation, thus less frequent direct involvement with large-caliber arteries and arterial bifurcations.[31,32]

Smoking in this sample showed a positive correlation with atheromatous disease in the earlier stages of the disease (increased IMI) and in the more advanced stages (presence of plaques with or without stenosis). This corroborates the studies, where smoking is associated with carotid alterations.[25,26]

Unlike in this sample, AF had a significant correlation with normal exams. This is in line with some research studies previously carried out. AF and other cardioembolic diseases are the main cause of stroke, most of the time not due to disease of the local arterial wall, but due to the formation of thrombi of cardiac origin.[33]

The main limitation of this study is the retrospective inclusion of individuals who received cervical Doppler, excluding all the patients that didn't do it.

Conclusions

There are no publicated data of our Alentejo population, a very old one with particular diet habits. In this study it was possible to characterize the correlation of non-modifiable risk factors such as advanced age, male sex and the presence of a personal history of brain and cardiovascular diseases with the increased occurrence of IMI. Male gender and modifiable risk factors such as hypertension, diabetes, dyslipidemia and smoking are related to more advanced stages of atherosclerotic disease, with the presence of atheromatous plaques with and without hemodynamic repercussions.

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