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Review

What is hidden behind the gender differences of carotid atherosclerosis?

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Abstract: This review article reveals possible causes that may underlie gender differences of carotid atherosclerosis: vascular anatomy, localization and morphology of atherosclerotic plaques, different effects and prevalence of known risk factors between genders (arterial hypertension, hypercholesterolemia, obesity, smoking, alcohol consumption, depression / stress). A separate place in the review is given to markers of inflammation and the protective effect of female sex hormones.

Keywords: gender differences, carotid atherosclerosis, risk factors, hypercholesterolemia, smoking, alcohol consumption, national characteristics.

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Introduction

Cardiovascular diseases remain the most common cause of death among population, accounting for more than 17.8 million cases annually, according to WHO statistics. Coronary artery disease is the leading cause of death worldwide accounting for 16% of deaths from all diseases of both men and women [1].

National statistics of ESC member countries for 2019 shows that cardiovascular diseases account for 2.2 million deaths among women and 1.9 million deaths among men. When analyzing the causes of cardiovascular mortality in European countries certain gender differences can be traced. Hence, the main cause of death from cardiovascular diseases is coronary artery disease, which accounts for 38% of deaths among women and 44% among men. Stroke is the second leading cause of death from cardiovascular disease in ESC member countries accounting for 26% of all deaths from cardiovascular disease among women and 21% among men [2].

WHO data on world mortality statistics also show that stroke is the second most common cause of death among all diseases accounting for 12% of all deaths of women and 8% of men [1].

Atherothrombosis, which is the cause of myocardial infarction and stroke, occurs when there is a substrate for its development, i.e., the formation of an atherosclerotic plaque in the corresponding vascular basin. According to static data, the formation of atherosclerotic plaque in the coronary arteries with the subsequent development of coronary artery disease is more often recorded among men [3].

As for the formation of atherosclerotic plaque in the basin of the carotid arteries in comparison with the coronary arteries, there is evidence of a more frequent detection of this pathology among women. At the same time, there are data confirming the relationship between the presence of carotid atherosclerosis not only with the risk of stroke and the progression of cognitive impairment, but also with an increase in overall mortality [4-6]. Atherosclerosis of the carotid arteries, especially in the presence of unstable atherosclerotic plaque, is associated with the development of ischemic stroke [7], including patients with nonvalvular atrial fibrillation [4].

At the same time, the contribution of various factors and their different effects on the formation of atherosclerosis in the coronary and carotid basins, in particular inflammatory and lipid biomarkers, are discussed [3, 8, 9].

Understanding the role of various risk factors, the influence of biomarkers, gender and age, combined with the use of imaging methods of examination, can help medical professionals better stratify patients at high risk of developing stroke and determine the optimal treatment approaches.

The aim of this review was to systematize and combine as much scattered data as possible from various studies on the analysis of factors affecting the development of carotid atherosclerosis, describe not only the influence of known risk factors and associated conditions, but also their gender differences. At the same time, one of the objectives of this review was to reflect the influence of important behavioral factors, alcohol consumption and tobacco smoking. In addition, this review attempts to take into account important territorial / ethnic factors, which were not previously described in the aspect of this problem (these data are given at the end of each section).

Differences in vascular anatomy

The formation of atherosclerotic plaques at the sites of arterial bifurcation can be explained in terms of hemodynamic laws and dependence on vascular anatomy in particular on the relative size of the main arterial vessel and its branches and outflow/intflow

area ratio. According to a number of studies, an atherosclerotic plaque stenosing the lumen of the carotid artery is more common for men, while the presence of atherosclerosis in the form of thickening of the intima-media complex (IMT) in the absence of stenosis is more common for women. This issue increases the likelihood of gender differences in the anatomy of the carotid artery bifurcation [10-16].

5395 patient angiograms were analyzed in the ESCT study (European Carotid Surgery Trial). Angiograms with stenosis >=50% were excluded to minimize secondary change. The diameters of the arteries were measured at points free from atherosclerotic lesions, and the following ratios were calculated: ICA / CCA, ECA / CCA, ICA / ECA, carotid bulb / CCA, and the outflow / inflow area ratio. Among 2930 angiograms with stenosis <50% the mean ICA / OCA ratio, ICA / ECA ratio, and outflow / inflow area ratio were greater among women than men (p<0.0001). Similar results were obtained when analyzing 622 angiograms, in the bifurcations of which no atheroma was recorded. Significant differences between men and women were also observed in the distribution of plaques: men were more likely to have maximal stenosis distal to the carotid bulb (odds ratio 2.29; 95% CI 1.33-4.01; P=0.001), while women were more likely to have ECA stenosis (odds ratio 1.54; 95% CI 1.30-1.85; P<0.0001) [17].

Gender differences in the anatomy of the bifurcation of the carotid artery are not limited only by the absolute size of the vessels despite the fact that the outflow/intflow area ratio is greater among women, and women on average have a larger ICA diameter than men. In another Chinese study, logistic regression analysis showed that a smaller lumen of carotid artery bifurcation was associated with an increased risk of unstable plaque, in contrast to a wider vessel diameter (OR 0.45 [95% CI, 0.25-0.81]; p=0.008) [7].

Differences in plaque localization

Gender differences in the location of atherosclerosis among asymptomatic patients with hyperlipidemia were revealed in the study performed by Mattina A et al. Coronary artery disease was more common for men, while a higher prevalence of carotid atherosclerosis was reported among women. When two vascular basins were affected, women had an increased prevalence of atherosclerosis of the femoral and carotid arteries, whereas men had a higher incidence of atherosclerosis of the coronary and femoral arteries [18].

In another Bavarian study, similar data were obtained that coronary artery disease was more common for men [19].

The SAMMPRIS study (Stenting and Aggressive Medical Management for Preventing Recurrent stroke in Intracranial Stenosis) included 451 patients with recent transient ischemic attack or stroke caused by severe (70-99%) stenosis of the main intracranial artery. An analysis of baseline demographic characteristics and risk factors for vascular disease was performed. Out of 449 patients included in the analysis 289 (64.4%) had stenosis in the anterior cerebral artery basin and 160 (35.6%) in the posterior cerebral artery basin. Gender was the characteristic that significantly differed between the patients with stenosis in the basin of the anterior and posterior cerebral arteries: men/women – 52.9%/47.1% versus 74.4%/25.6%, p<0.001 [20].

Differences in plaque morphology

Analysis of plaque morphology is important for predicting atherothrombotic events.

Hellings WE et al studied samples obtained from carotid endarterectomy of 450 patients (135 women, 315 men). The excised atherosclerotic plaques were analyzed for macrophages, smooth muscle cells, collagen, calcification, and for the presence of a thrombus on the surface of the plaque lining. Atherosclerotic plaques were classified into three phenotypes depending on the cellular composition and the amount of cholesterol.

Atheromatous plaques (>40% cholesterol) were less common for women than men (22% versus 40%; P<0.001). In addition, plaques obtained from women were more likely to show weak macrophage staining (11% versus 18%; P=0.05) and strong smooth muscle cell staining (38% versus 24%; P=0.001). The observed differences were most pronounced in asymptomatic women, who had the most stable plaques, while atheromatous plaques were observed in only 9% of cases compared with 39% of asymptomatic men (P=0.02). In addition, most of the plaques obtained from asymptomatic women showed high levels of smooth muscle cells (53% versus 30%; P=0.03) and high levels of collagen (55% versus 24%; P=0.003). In conclusion of this study, the authors stated that carotid artery plaques obtained from women have a more stable, less inflammatory phenotype than men regardless of the clinical picture and risk profile of cardiovascular disease. Asymptomatic women have the highest prevalence of stable plaques [21].

In another work that studied the morphology of atherosclerotic plaques, German researchers obtained data that male gender was associated with greater cellularity (odds ratio [OR], 1.56; P=0.003), a greater number of inflammatory infiltrates (OR, 1, 75; P<0.001) and more neovascularization (OR, 1.47; P=0.010), but with a lower incidence of calcification (OR 0.78; P=0.090). A polynomial regression model showed that age, gender, and history of neurological symptoms were significantly associated with specific types of plaques (P=0.009, P<0.001, and P=0.017, respectively). The morphology of atherosclerosis of the carotid arteries differed between men and women and changed with age [22].

Influence of risk factors: arterial hypertension

The fact that one of the main risk factors for the development of carotid atherosclerosis is arterial hypertension is known from observational studies carried out in the mid-1990s [11, 15].

But recent studies began to pay attention to gender differences in the effect of hypertension on the development of atherosclerosis. Tromba L et al confirmed in their study that the most frequent risk factor for the development of this pathology is arterial hypertension. At the same time, it was revealed that the presence of atheromatous plaques significantly correlated with age for both genders, and carotid plaques were more often detected among men than women. The genders varied significantly in the location of plaques, echogenicity, echo structure, and intracranial circulation. The authors of the study concluded that risk factors, in particular arterial hypertension, affect the formation and spread of atherosclerotic plaques in the carotid arteries more among men than women [10].

Su TC et al found that the main determinants for an increase in CCA-IMT for women 45-74 years old were systolic blood pressure and history of hypertension requiring drug treatment, in contrast

to men, according to multivariate regression analysis in their study. SBP was an important determinant of CCA-IMT for people of both genders over 75 [23].

In addition, high SBP is a risk factor for the development of unstable atherosclerotic plaque [24].

In the Finnish study, paradoxical data were obtained that hypertension as a risk factor for carotid atherosclerosis begins to manifest itself already from childhood. The relative risk of detecting initial carotid atherosclerosis adjusted for age and gender was 1.51 (95% CI, 0.99-2.32) for high SBP in childhood [25].

It is interesting to refer to data from population statistics. The ECVDS data show that the prevalence of hypertension in all ESC member countries was lower among women than men with mean detection rates of 22.3% (IQR 15.5-23.9%) and 27.0% (IQR 24.2-33.6%), respectively. Average blood pressure levels vary significantly across countries: average SBP values of 115 mm hg for women were registered in Switzerland compared to 130 mm hg in Moldova; for men – 120 mm hg in Turkey compared to 137 mm hg in Croatia, Lithuania, and Slovenia [2].

Influence of risk factors: hypercholesterolemia

Hypercholesterolemia is a well-known and well-studied risk factor for the development of atherosclerosis. Human often meets with it from a very young age, which was confirmed in the paper of Koskinen JS et al. This study included 2,653 children 3 to 18 years of age. Carotid plaque, defined as a focal structure of the arterial wall protruding into the lumen >50% compared to the adjacent IMT, was present in 3.3% of participants (88 of the study cohort).

The relative risk of detecting initial carotid atherosclerosis adjusted for age and gender for childhood dyslipidemia was 3.03 (95% CI, 1.76-5.21). Childhood dyslipidemia remained an independent prognostic factor for carotid atherosclerosis in analyzes adjusted for risk factors in adults and a family history of coronary artery disease [25].

These findings support the need to strengthen prevention of risk factors from early childhood and demonstrate the usefulness of screening according to the guidelines-based thresholds for identifying children at increased risk of atherosclerosis in adulthood.

In an Italian study, 974 participants 25-88 years of age (478 men and 496 women) underwent a clinical examination (including a lipid spectrum) and ultrasound examination of the carotid arteries with IMT measurement, assessment of arteries diameter and size of atherosclerotic plaques. It was found that the most frequent risk factor for the detection of carotid atherosclerosis along with arterial hypertension is hypercholesterolemia. At the same time, men had high average IMT values of the carotid arteries and a high prevalence of atherosclerotic plaques more among men than women [10].

Chinese researchers obtained the data that abnormal increases in total cholesterol and apolipoprotein B levels predominantly among men were risk factors for unstable atherosclerotic plaque (OR 3.693 and 39.215, respectively) [24].

Kozáková M et al had a medical check up of 366 men and 422 women (ages 30 to 60) who underwent B-mode ultrasound examination of the carotid arteries at the beginning of the study and after 3 years of follow-up. IMT in 3 segments of the carotid artery was significantly higher among men than women ($p<0.0001$ for all segments). Differences between men and women when analyzed according to age decades disappeared in the 6th decade. If age was the main determinant of IMT for women then men, in addition to this, a statistically significant effect on IMT increase was high level of LDL cholesterol (which was not confirmed for women). In this study, it was stated that the progression of IMT did not correlate with the other established risk factors for cardiovascular diseases, their short-term changes or family predisposition to CVD [26].

The Tromso study examined 6408 men and women 25 to 84 years of age who underwent ultrasound examination of the carotid arteries and identified the main risk factors for cardiovascular disease. In this study, total and HDL cholesterol were independent predictors of IMT for both genders. Triglyceride levels were associated with IMT independent of HDL cholesterol only among women. The magnitude of the association between most risk factors and TIM did not differ depending on age, but the effect of triglycerides was more pronounced at an older age [27].

Shen H et al found that sdLDL-C level was significantly higher among men than women ($p<0.05$), and there was an effect of age on sdLDL-C level ($p<0.05$). After adjusting for the influence of age, gender and other traditional CVD risk factors according to multiple regression analysis, sdLDL-C was found to be a significant factor for increasing the IMT of the carotid arteries ($\beta=0.437$, $p<0.001$) [28].

ECVDS data show that the average age-standardized prevalence of hypercholesterolemia (>6.2 mmol/L) averaged across ESC member countries for 2008 was 15.6% (IQR 12.1-18.9%) for women and 14.3% (IQR 9.6-18.6%) for men. At the same time, the pronounced differences between countries in the prevalence of hypercholesterolemia among the population attracted attention: <10% in such countries as Bosnia and Herzegovina, Georgia, Kyrgyzstan, Moldova and Turkey; in contrast to statistics in Scandinavian and Central European countries (Norway, Finland, Denmark, Iceland, Belgium, France, Germany, Ireland and the UK), where the prevalence of hypercholesterolemia was more frequent and leveled to >20% [2].

Influence of risk factors: obesity / metabolic syndrome

In addition to age and gender, one of the risk factors for augmented IMT of the carotid arteries is an increased body mass index at a young age. Such data were obtained among people 35-44 years of age by Su TC et al in their study [23].

To assess the association between weight change and subclinical carotid atherosclerosis of healthy but overweight or obese participants a cohort study was conducted that included 3117 healthy overweight or obese adults who had no baseline metabolic syndrome or insulin resistance. During 12,248 person-years of follow-up (median 3.42 years), 747 participants developed carotid atherosclerosis. The proportions of participants without weight change, weight loss from 0.1% to 4.9%, and weight loss ≥5% during follow-up were 47.0%, 44.4% and 8.6%, respectively. The fully adjusted risk ratios for detecting carotid atherosclerosis among participants with a weight loss of 0.1% to 4.9% and ≥5% compared with participants without weight loss or gain were 0.84 (95% CI, 0.72-0.98) and 0.66 (95% CI, 0.50-0.87), respectively. In this study, it was confirmed that weight loss was associated with a lower incidence of carotid atherosclerosis in prospective follow-up among healthy men and women who are overweight or obese [29].

In the study performed by Łoboz-Rudnicka M et al., it was found that women had lower IMT values than men (0.54 mm

versus 0.60 mm, P=0.011), which was most pronounced over 45 years old. In addition to age (β=0.497, P<0.001), the body mass index (β=0.195, P=0.006) was an independent determinant of IMT for the entire group according to multiple regression analysis. For women, significant factors were type 2 diabetes (b=+0.111, P<0.01), body mass index (b=+0.007, P<0.05), increased waist circumference (b=+0.092, P<0.01) and metabolic syndrome (b=+0.071, P<0.05) in addition to age (b=+0.008, P<0.0001). For men, age was the only independent factor determining IMT (β=0.669, P<0.001) [30].

Another study also confirmed that the IMT of the carotid arteries was increased in the group of patients with metabolic syndrome compared with the control group without metabolic syndrome (p=0.001). A significant association was found between metabolic syndrome and carotid IMI among women but not men (p=0.002 and p=0.364, respectively) by logistic regression analysis. After adjusting for age, body mass index, the presence of arterial hypertension and hyperlipidemia this relationship was significant only for women (p=0.011) regardless of the presence of the listed risk factors. Thus, it was concluded that metabolic syndrome is a stronger risk factor for subclinical atherosclerosis for women than men [31].

According to the ESC statistics, approximately one out of five adults (both women and men) is obese (>30 kg/m2). Obesity has territorial and gender differences. Obesity among women is especially common in Egypt and Libya while obesity among men is more common in such countries as Hungary, the Czech Republic and the United Kingdom. The average BMI for women varies from 23.7 kg/m2 in Switzerland to 31.4 kg/m2 in Egypt and among men from 24.7 kg/m2 in Algeria to 28.2 kg/m2 in Hungary [2].

Influence of risk factors: smoking

Smoking is closely associated with the development of cardiovascular disease. Smoking prevalence remains high in both developed and developing countries. It is known that smoking and coronary heart disease is more common for men [19, 32]. Smoking in childhood increases the risk of carotid atherosclerosis by almost 2 times: the relative risk adjusted for age and gender is 1.93 (95% CI, 1.26-2.94) [25].

The ELSA-Brasil study (Brazilian Longitudinal Study of Adult Health) investigated the association of smoking status, time since quitting smoking, and markers of inflammation with subclinical atherosclerosis. The study included 14 103 participants without clinical manifestations of cardiovascular disease, who were analyzed for smoking status, high sensitivity C-reactive protein (hsCRP), carotid intima-media thickness, ankle-brachial index and coronary artery calcium content (CAC). The cohort included 1,844 smokers, 4,121 ex-smokers and 8,138 never smokers. The average age was 51.7±8.9; 44.8% were men. Current smokers had significantly higher hsCRP levels (β=0.24, 0.19-0.29 mg/L; p<0.001), carotid intima-media thickness (β=0.03, 0.02-0.04 mm; p<0.001), ankle-brachial index ≤1.0 (OR 2.52; 95% CI, 2.06-3.08; P<0.001) and CAC>0 (OR 1.83; 95% CI, 1.46-2.30; P<0.001) compared with never smokers. Smoking burden (years of smoking) was significantly associated with hsCRP (p=0.006) and CAC (p=0.002) among former and current smokers. Among former smokers hsCRP and carotid IMT levels were lower with increasing time after smoking cessation (p<0.01). Smoking intensity (number of cigarettes per day) was positively associated with hsCRP (p<0.001) and CAC>0 (p=0.03) levels among current smokers. Thus, there was a strong association between smoking status, smoking burden and intensity with markers of inflammation (hsCRP) and subclinical atherosclerosis [33].

The Japanese study aimed to investigate the relationship between cigarette smoking and carotid intima-media thickness. Among the 1209 participants included in the study 450 participants (37.2%) were smokers (including both former and current smokers). Mean IMT values did not differ between the groups of smokers and never smokers. However, the incidence of high-risk carotid atheroma, including ulcerated plaque, was significantly higher among smokers than never smokers (30.4% versus 23.6%, p=0.009). Smoking was independently associated with high risk atheroma (odds ratio 1.384, 95% CI 1.019-1.880; p=0.038). The authors concluded that the development of high-risk carotid atheroma may precede IMT thickening among smokers, suggesting a new understanding of the pathological mechanism underlying the development of cardiovascular events due to tobacco smoking [34].

It was confirmed that current smokers had a significantly higher risk of subclinical atherosclerosis in all 4 vascular basins compared with never smokers in the SESSA study (Shiga Epidemiological Study of Subclinical Atherosclerosis). Those who quit smoking had an increased chance of detecting carotid atherosclerosis and atherosclerosis of the aortic valve (OR 1.94 [1.13-3.34] and 2.55 [1.45-4.49], respectively). A correlation relationship between the pack-years index and daily consumption was observed especially for IMT increase and detection of carotid atherosclerosis both among current and former smokers [35].

There was a higher prevalence of tobacco smoking among men compared to women: 26.5% (IQR 21.7-33.9%) vs. 15.0% (IQR 12.1-18.5%) in all 29 ESC member countries (according to 2014 data). The highest prevalence of tobacco smoking among men (over 40%) was noted in Latvia, Albania, Armenia, Belarus and Turkey. The prevalence of smoking among women of more than 20% was recorded in Austria, Hungary, Greece, Latvia, France and Croatia [2].

Thus, although the above studies do not describe direct gender differences in the effect of tobacco smoking on the development of carotid atherosclerosis, it can be argued that the fact of a significantly higher prevalence of smoking among men thus has a greater impact as a risk factor. Moreover, there are suggestions that smoking may have additional mechanisms of influence on changes in the lipid profile among patients with arterial hypertension and cardiovascular diseases [36].

Smoking is a strong but preventable risk factor for cardiovascular disease, and this indicates the need for more active promotion of prevention programs among the population to quit smoking.

Influence of risk factors: alcohol

Historical epidemiological data indicate a protective effect of moderate alcohol consumption on cardiovascular events [37-39]. Most studies lean towards the benefits of moderate red wine consumption since it contains polyphenols (quercetin and resveratrol), which have antioxidant properties that can have an angioprotective effect [40-42]. This concept was named "French paradox" in the scientific medical literature of the late 20th century [43]. However, the results of scientific publications in recent years state that moderate alcohol consumption reduces the

risk of myocardial infarction and increases the risk of cerebral stroke [44-45].

The available data of the effect of alcohol consumption on the development of carotid atherosclerosis in the scientific medical literature are not as numerous as for other risk factors. In this regard, the results of a study carried out in Hamburg (Germany) are of particular interest. The aim of the STRATEGY study (Stress, Atherosclerosis and ECG Study) was to investigate the relationship between alcohol consumption and IMT among a healthy population. Laboratory indicators, anthropometric data, diet and physical activity were assessed for 106 men and 107 women (evenly distributed by age groups ranging between 30 and 70) in a cross-sectional study. Men showed a significant positive correlation between daily alcohol consumption and IMT ($p<0.0001$), whereas women did not have a significant positive correlation. The type of alcoholic beverage consumed did not influence this finding. The mean IMT was significantly higher among men with alcohol consumption above the upper limit of 20 g/day than ones with alcohol consumption <20 g/day ($p<0.001$). According to a stepwise linear regression model adjusted for age and generally accepted risk factors, IMT increases by 0.0253 mm by 21.4 g/day of alcohol consumption among men ($p<0.05$). The STRATEGY study revealed a positive relationship between alcohol consumption and IMT of the carotid arteries among healthy men 30-70 years of age [46].

The analysis of the relationship between alcohol consumption and carotid atherosclerosis was carried out in a cohort of participants in the ARIC study (The Atherosclerosis Risk in Communities) 45 to 64 years of age. Alcohol consumption in the ARIC sample was generally low. There were no statistically significant relationships between alcohol consumption and IMT of the carotid artery. The adjusted mean carotid IMT among white women tended to be higher in low- to moderate-dose alcohol users than among those who never drank alcohol, but the difference between categories was at the border of statistical significance ($p=0.04$) [47].

At the same time, no gender differences were obtained for this factor for young people in the Finnish study (The Cardiovascular Risk in Young Finns Study). The study included 2074 patients 24-39 years of age, who analyzed alcohol consumption and determined the IMT of the carotid arteries. Among non-alcoholic participants, consuming 0 to 2, 2 to 4, or ≥4 drinks per day, the corresponding carotid IMT values were 0.57±0.004, 0.59±0.003, 0, 59±0.006 and 0.60±0.012 mm ($p<0.0001$). This direct relationship between alcohol consumption and IMTI in the multivariate regression model did not depend on age, gender, and other risk factors for cardiovascular disease (such as hypertension, LDL cholesterol, BMI, smoking, CRP). The frequencies of wine drinking or strong alcohol beverages were directly correlated with an increase in IMT in models adjusted for age, sex and risk factors. The researchers concluded that alcohol consumption may have pro-atherogenic effects among young healthy adults [48].

Similar results were found in the Cardiovascular Health Study, which enrolled 5888 patients over the age of 65. Those who drank 1 to 6 drinks per week had an inverse relationship with carotid atherosclerosis and those who drank 14 or more alcohol drinks had a significant positive correlation with the detection and progression of carotid atherosclerosis compared with study of the participants who abstained from drinking alcohol [49].

The Korean Dong-gu Study dedicated to this issue included 4302 people (1577 men and 2725 women) 50 years old and more. Daily alcohol consumption was determined by the amount and frequency of alcohol consumption. Intima-media thickness of the common carotid artery and common carotid bulb were negatively correlated with alcohol consumption after adjusting for major risk factors for cardiovascular disease among men ($p=0.009$ and $p=0.038$, respectively). The odds ratio (OR) for detecting carotid plaques was significantly higher for men consuming >40.0 g/day (OR=1.81, 95% CI=1.13-2.91). A significant correlation was observed between alcohol consumption and the presence of atherosclerotic plaques in the carotid arteries ($p=0.027$). In this study, no correlations were found between the IMT of the carotid arteries, the presence of atherosclerotic plaques in the carotid artery, and alcohol consumption among women. The results of this study show that alcohol consumption is inversely related to the IMT of the carotid arteries and is positively associated with carotid plaques among men but not women [50].

Similar results were obtained earlier in the Three-City Study: a statistically significant relationship between alcohol consumption and an increase in IMT of the carotid arteries was confirmed only for men ($p=0.02$) [51].

In addition, it was shown that binge drinking was associated with increased progression of atherosclerosis during the 11-year follow-up period among middle-aged men regardless of the total alcohol consumption [52].

Analysis data for 2016 among all ESC member countries show that fewer women than men (55.1% (IQR 28.9-62.9%) vs. 79.4% (IQR 56.1-84.2%)) consumed alcohol in the previous 12 months. The average alcohol consumption among women was correspondingly lower compared to men (4.1 (IQR 2.5-5.1) vs. 16.8 (IQR 11.8-19.4) liters per capita population per year). Age-standardized median prevalence of heavy drinking was also lower among women compared with men (15.0% (IQR 7.8-20.1%) vs. 47.4% (IQR 32.0-55.9%)). The indicator value of >60% was registered for men in the Baltic countries (Estonia, Latvia, Lithuania), the Czech Republic, Luxembourg and Slovenia. These rates were also high among women in these countries and exceeded 30% for women in Latvia, Lithuania and Luxembourg [2].

Influence of risk factors: depression / stress

The fact that depression and stress can be risk factors for the development of cardiovascular diseases and their complications has long been known.

The analysis of the relationship of known risk factors with the subsequent development of myocardial infarction was carried out in a large multicenter INTERHEART study, which included 24,767 people from 52 countries. The value of the relative risk of developing myocardial infarction for the factor of depression / stress (validated on the basis of a special questionnaire) exceeded in significance of such known risk factors as arterial hypertension and diabetes mellitus (RR 2.67 versus 1.62 and 2.37, respectively). In addition, it was noted that the combination of various factors significantly increased the risk of MI. Moreover, among the participants in this study there was a higher prevalence of depression / stress among women compared with men (40% vs. 25%) [53, 54].

Stress as a risk factor can exert its negative influence not only by affecting the nervous system and neurohumoral factors but also mediated through others including lipid factors [55].

The burden of severe chronic disease can be a cause for depression or constant stress, which affects the progression of carotid atherosclerosis what was confirmed in a prospective study of women with HIV in an American study [56].

Stress is often present at a workplace. Research confirms that stress at work associated with an increased risk of atherosclerotic plaque formation in the carotid artery (adjusted OR=3.21, p=0.019). At the same time, social support measures, prevention of stress and treatment of depressive disorder can help reduce the progression of cardiovascular disease [57].

Wu J H et al. conducted a study on this issue. A total of 2947 metallurgical plant workers were selected as subjects, who underwent a medical examination and filled out specialized validated questionnaires (Job Content Questionnaire (JCQ) and Effort-Reward Imbalance (ERI)). According to the results of ultrasound examination of the carotid arteries, the patients were divided into the group of persons without pathology (n=2013), the group of those who had an increase in the thickness of the intima-media of the carotid artery (n=277), the group of those who had a stable atherosclerotic plaque (n=236) and the group with registered unstable plaque (n=421). There were significant differences between the groups in terms of gender, education level, marital status, shift work, smoking, alcohol consumption, age and employment term (p<0.05). On the JCQ scale, 761 (25.8%) experienced no stress, 959 (32.5%) had mild stress, 699 (23.7%) had moderate stress, and 528 (17.9%) had severe stress. According to the ERI scale, 2526 (85.7%) had a high degree of workload and low remuneration, and 421 (14.3%) did not have a high degree of workload and low remuneration. Moderate stress (odds ratio [OR]=1.695), severe stress (OR=5.443) and shift work (OR=1.784) were significant risk factors for unstable atherosclerotic plaque. In the conclusion of the study, the authors claimed that occupational stress can be the cause of the development of carotid atherosclerosis [24].

Lee YH et al. investigated the association of depressive symptoms with intima-media thickness of the carotid arteries and the presence of atherosclerotic plaques in a survey of the Korean population. The analysis included a total of 7,554 men and women 45 to 74 years old without cardiovascular disease. Symptoms of depression were assessed at the Center for Epidemiological Research Depression Scale (CES-D). Subjects with a score of ≥16 on this scale were classified as having clinically significant depressive symptoms. Carotid ultrasound was used to measure the mean IMT of the carotid artery and to determine the presence of atherosclerotic plaques. A significant association between depressive symptoms and TIM was observed only among women. After adjusting of established risk factors for cardiovascular disease, IMT values were significantly higher among women with depressive symptoms than ones without depressive symptoms (mean difference 0.011±0.004 mm; 95% CI 0.003-0.019 mm). The adjusted risk among women with depressive symptoms of detecting an elevated IMI (≥1.0 mm) was significant (OR 1.63; 95% CI 1.16-2.30). No significant association between depressive symptoms and the detection of atherosclerotic plaques in the carotid artery was observed at either gender. This study found a significant association between depressive symptoms and IMI among middle-aged and older women [58].

The Whitehall II study included 2822 men and 1112 women (mean age 61±6). They determined lipid levels and the thickness of the intima-media of the carotid arteries. The participants completed the General health questionnaire and the Center for Epidemiologic Studies depression scale. Linear regression was used to examine the relationship between depression / anxiety and intima-media thickness. 1461 participants were categorized as depressed / anxious. The relationship between depression / anxiety and intima media thickness differed between men and women. For men, intima-media thickness was significantly associated with dyslipidemia (p=0.002), but not with depression / anxiety (p=0.29). For women, both dyslipidemia and depression / anxiety were independently associated with intima-media thickness (p=0.028 and p=0.031). The highest intima-media thickness was among women with depression / anxiety and dyslipidemia. In conclusion, the authors stated that depression / anxiety is associated with increased intima-media thickness among women but not men. Women with depression and / or anxiety and dyslipidemia are potentially at the greatest risk of cardiovascular disease [59].

Thus, answering the question whether depression and stress affect the progression of carotid atherosclerosis to a greater extent for women than men, one can give an affirmative answer [60].

Inflammatory markers: c-reactive protein

It is known that inflammatory markers, in particular highly sensitive C-reactive protein (hsCRP), are associated with atherosclerosis and cardiovascular diseases. An increased level of highly sensitive C-reactive protein is a risk factor for detecting unstable atherosclerotic plaque in the carotid artery (OR=1.632) [24].

There is information on the importance of gender differences for the relationship between hsCRP and the progression of early stages of carotid atherosclerosis.

Halvorsen DS et al. surveyed 5,341 people in the Tromso Study to determine whether markers of inflammation are associated with the morphology of carotid plaques. 3205 had carotid plaques on ultrasound of the right carotid artery, and the plaque area and echogenicity of the plaque were determined. The white blood cell count (WBC), fibrinogen and C-reactive protein (CRP) as well as other risk factors for cardiovascular disease were analyzed. Women and men with atherosclerotic plaques in the carotid artery had significantly increased WBC and fibrinogen levels but not CRP compared with individuals without atherosclerotic plaques. All inflammatory markers were significantly associated with plaque area among men. WBCs were significantly associated with plaque echogenicity among women, while no association was found between fibrinogen and CRP and plaque echogenicity for either gender. This cross-sectional study showed gender-dependent differences in associations between indicators of carotid atherosclerosis and inflammatory markers [61].

The effect of hsCRP on early progression of carotid atherosclerosis and major vascular risk factors for men and women (n=3387) was studied in a prospective population-based INVADE study (Intervention project on cerebrovascular diseases and dementia in the community of Ebersberg, Bavaria). The thickness of the intima-media of the carotid artery and hsCRP was determined at baseline and after 2 years of follow-up in addition to the main risk factors. In the prospective part of the follow-up, data from 2346 people were available for analysis. In this study population, women were older and had higher levels of systolic blood pressure and cholesterol. Baseline carotid IMT was

significantly higher among men compared to women (0.82 mm; 95% CI 0.812 to 0.834 mm vs. 0.77 mm; 95% CI 0.763 to 0.779 mm; P<0.0001). The increase in IMT of the carotid arteries after adjustment for risk factors was significantly associated with hsCRP among women (p=0.006) but not men (p=0.39). The authors of the study concluded that the relationship between hsCRP and the progression of early carotid atherosclerosis shows gender differences [19].

The Jackson Heart Study questioned whether high-sensitivity C-reactive protein (hsCRP) is useful as a biomarker for different obesity phenotypes and phenotypes at increased risk of subclinical atherosclerosis among African Americans (n=4682). Study participants were divided into 4 phenotypes based on the National Heart, Lung and Blood Institute definition of obesity (BMI≥30 or BMI 25-30 with waist circumference> 102 cm among men and> 88 cm among women) and activity inflammation with the result of hsCRP≥2 mg/L.

The relationships between obesity phenotypes and subclinical atherosclerosis as measured by carotid intima-media thickness were analyzed using multiple regression analysis. The prevalence of obesity or its equivalent was 65%, of which 30% showed no signs of active inflammation. 37% of non-obese people had elevated hsCRP levels; hsCRP≥2 mg/L identified a subgroup of individuals with higher carotid intima-media thickness among non-obese men (adjusted mean difference=0.05, 95% CI 0.02, 0.08 mm) compared with their controls that had normal hsCRP levels. No association was found between hsCRP and carotid intima-media thickness for women. Thus, hsCRP analysis was useful in identifying a subgroup of non-obese males with higher carotid intima-media thickness [62].

It is believed that the activity of inflammation in an atherosclerotic plaque may have a greater predictive value than the plaque size. According to numerous studies, the total area of atherosclerotic plaques and level of inflammatory markers are generally higher among men than women. These markers allow predicting the risks of cardiovascular events [16].

Protective effect of female sex hormones and the reverse effect of menopause

Young women are relatively protected from cardiovascular disease but by the seventh decade the incidence of myocardial infarction among women eventually exceeds that among men, suggesting the relationship between gender and age [16].

Observational studies show that the risk of cardiovascular disease increases during menopause. The Chinese Multi-provincial Cohort Study enrolled 879 women. The age of menopause was classified as <40 (premature menopause), 40-44 (early menopause), 45-49 (relatively early menopause), 50-51 (standard menopause), and >51 (relatively late menopause). Of the 879 women included (mean age initially 48.6+8.1 years), 573 (65.2%) were diagnosed with atherosclerotic plaques in the carotid artery and 430 (48.9%) had intima-media thickening. Menopause was significantly associated with the risk of developing carotid plaques (HR 1.93, 95% CI 1.05-3.54; p=0.03) after adjusting for baseline age, age at menopause, oral estrogen use associated with menopause and traditional risk factors for cardiovascular disease during menopause. Menopausal women regardless of age at menopause had an increased risk of carotid atherosclerosis [63].

The MsHeart study involved 304 women between the ages of 40 and 60. They analyzed the effect of sex steroids on the carotid plaque and its characteristics. All participants underwent an ultrasound examination of the carotid arteries and an extensive hormonal blood test: estrogen (E1), estradiol (E2), testosterone (T), sex hormone binding globulin (SHBG) and free testosterone (FT). The presence of carotid plaque in the carotid arteries was confirmed for 46% of the study participants (n=141). The volume of carotid plaques (number of plaques, total plaque area (TPA)) and characteristics (calcification, echogenicity) were determined using semi-automated software. SHBG was inversely proportional to TPA (OR 0.39; 95% CI 0.21, 0.74). Higher FT levels were associated with higher TPA (OR 2.89; 95% CI 1.31, 6.37). A higher E1 was associated with echogenicity of the plaque (OR 2.31; 95% CI 1.26, 4.33), which is characteristic of a more stable plaque. The study authors concluded that SHBG and FT are associated with TPA, while E1 is connected with plaque echogenicity, suggesting that these hormones play different roles in the development of carotid plaques [64].

Hormone therapy (HT) may slow the accumulation of epicardial adipose tissue and the progression of atherosclerosis in different ways, depending on the particular hormone therapy agent or route of administration. The aim of the KEEPS Study (Kronos Early Estrogen Prevention Study) was to assess the effect of different oral and transdermal HT preparations on the association between epicardial adipose tissue and the progression of carotid atherosclerosis, as measured by carotid intima-media thickness (CIMT), among women in recent menopause. KEEPS was a randomized, placebo-controlled study evaluating the effects of oral conjugated estrogens (o-CEE) 0.45 mg/day or transdermal 17β-estradiol (t-E2) 50 μg/day compared to placebo during 48 months of observation. Increases in CIMT, epicardial adipose tissue (EAT), and paracardial adipose tissue (PAT) volume were quantified by computed tomography. A total of 467 women (mean age [SD] 52.7 [2.5]; 78.2% whites; 30% in the o-CEE group, 30.8% t-E2, 39.2% placebo) were included in the study. EAT and PAT changes were not associated with CIMT progression; however, the treatment prescribed significantly changed the association between PAT change (but not EAT) and CIMT progression. In the o-CEE group, the corrected progression of CIMT was 12.66 μm (95% confidence interval [CI] 1.80, 23.52) lower than in the t-E2 group (P=0.02), and 10, 09 μm (95% CI 0.79, 19.39) lower than placebo (P=0.03), according to an increase in PAT by 1-SD. Thus, compared to t-E2, o-CEE appears to slow down the adverse effect of increased PAT on the progression of atherosclerosis [65].

The goal of the Italian study was to examine the number and function of endothelial progenitor cells (EPCs) depending on cardiovascular risk, gender and reproductive status. According to flow cytometry data among 210 healthy participants, CD34 (+) KDR (+) EPC levels were higher among fertile women than men but did not differ between postmenopausal women and men of the same age. These gender differences were reflected in cardiovascular profile, carotid intimal thickness and blood flow-mediated brachial artery dilatation. Moreover, EPCs and soluble c-kit ligand were altered in phase with the menstrual cycle in ovulatory women, suggesting cyclical bone marrow mobilization. EPCs grown from healthy female donors were more clonogenic and adhesive than male EPCs. Treatment with 17-beta-estradiol stimulated proliferation and adhesion of EPCs through estrogen receptors. In conclusion of the study, the authors stated that EPCs are cyclically mobilized among fertile women, probably providing a pool of cells for endometrial homeostasis. As a result, higher EPC levels among women than men reflect the profile of the cardiovascular system

and may represent one of the defense mechanisms of the fertile female population [66].

The rapid increase in risk factors for cardiovascular disease among women after age of 55 weakens the advantage of women in terms of CCA-IMT compared to men. The gender difference in the CCA-IMT indicator levels off after reaching the age of 75 [23].

Conclusion

Thus, the data obtained indicate that there are many factors behind the gender differences in carotid atherosclerosis: differences in vascular anatomy, localization and morphology of atherosclerotic plaques, different influence and prevalence between the genders of known risk factors (arterial hypertension, hypercholesterolemia, obesity / metabolic syndrome, smoking, alcohol consuption, inflammatory markers, depression / stress) (see *Table* 1). A separate and significant place is occupied by the protective effect of female sex hormones and the inverse effect of menopause. All of these factors have polymodal and interrelated influences, which also have certain national and territorial gender differences.

Conflict of interest

The author declares no conflicts of interest regarding this publication.

Table 1. Gender differences in carotid atherosclerosis

Sign	*Gender*
Vascular anatomy	
ICA / CCA ratio is greater	among women [17]
ICA diameter is on average larger	among women [17,25,33]
Localization of atherosclerosis	
IMT increase in the absence of CAS	more common in women [10-16]
The presence of AP in CA (CAS)	more common in men [10-17,61,67]
Stenosis in the posterior cerebral artery basin (compared to the anterior cerebral artery)	more common in men [20]
Atherosclerosis of the coronary arteries	more common in men [3,18,19,32]
Morphology of atherosclerotic plaque in the carotid artery	
Atheromatous plaques	more common in men [21,22,61]
Stable plaque rich in collagen and smooth muscle cells	more common in women [21,22,61]
Influence of risk factors: arterial hypertension	
Prevalence of hypertension	more common in men [2,16]
Effect of arterial hypertension on CAS formation	more common in men [14,15]
High SBP increases the risk of unstable AP	both sexes [24]
Influence of risk factors: hypercholesterolemia	
A significant increase in total cholesterol is a predictor of unstable plaque detection	more common in men [24]
LDL-C affects IMT increase and plaque formation	more common in men [26]
High triglycerides levels affect IMT increase	more common in women [27]
High sdLDL-C levels affect IMT increase	more common in men [28]
Influence of risk factors: obesity / metabolic syndrome	
Increased BMI is a risk factor for IMT increase	more common in women [23,30]
Diabetes mellitus is a risk factor for IMT increase	more common in women [30]
Metabolic syndrome is a risk factor for IMT increase	more common in women [30,31]
Influence of risk factors: smoking	
Prevalence of smoking	more common in men [2,12,19,32]
Smoking is a risk factor for unstable plaque detection	both sexes [34]
Influence of risk factors: alcohol	
Prevalence of alcohol consumption	more common in men [2]
Daily alcohol consumption correlates with IMT increase	in men [46,50,51]
Daily alcohol consumption correlates with AP detection in CA	in men [49,50,52]
Influence of risk factors: stress / depression	
Prevalence of depression	more common in women [53,54]
Severe stress is a risk factor for developing unstable plaque	more common in men [24]
Depression is a risk factor for IMT increase	among women [58-60]
Influence of Risk Factors: markers of inflammation	
Increased CRP level is a risk factor for unstable plaque	both sexes [8,24]
The increased level of inflammatory markers correlates with the total area of AP in CA	more common in men [16,61]
Increased CRP level is a risk factor for IMT increase	whites: in women19/african-americans: in men [62]
Influence of risk factors: menopause	
Menopause is a risk factor for detecting AP in CA	in women [63,64]
Oral estrogens slow the progression of carotid atherosclerosis	in women [65]

AP, atherosclerotic plaque; CA, carotid artery; CCA, common carotid artery; ICA, internal carotid artery; IMT, intima media thickness; CAS, carotid artery stenosis; SBP, systolic blood pressure; BMI, body mass index; CRP, C-reactive protein.

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