Review

by Prof. Dr. Ivan Tomov Gruev, PhD,

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for the dissertation of Dr. Elitsa Rashkova Gerova - Micic

on the topic: "Multifocal atherosclerosis - diagnostic and prognostic markers in different vascular basins", for obtaining the educational and scientific degree "PhD" in the field of higher education 7. Health and sports, professional field 7.1. Medicine, doctoral program "Angiology", research unit: Clinic of Angiology, "Acibadem City Clinic UMHAT Tokuda" EAD. The review was prepared on the basis of an order of the Executive Director and the procurator of Acibadem City Clinic UMHAT Tokuda EAD № 15-05-71 / 04.04.2022.

I declare that in connection with the present work I have no conflict of interest and I do not establish evidence of plagiarism.

Dr. Elitsa Rashkova Gerova - Micic is a full-time doctoral student in the doctoral program "Angiology" at the Clinic of Angiology, Acibadem City Clinic UMHAT Tokuda EAD. She graduated from a language school in Plovdiv and MU - Sofia. He has a specialty in angiology. She has worked at Sofiamed University Hospital and Acibadem City Clinic UMHAT Tokuda EAD.

Cardiovascular disease (CVD) is the leading cause of death worldwide. In Europe, CVDs cause more than 4 million deaths a year and cause 42% and 51% of deaths, respectively, among men and women. In Bulgaria this percentage is even higher - over 60% for both sexes! Atherosclerosis is a multifocal process, ie. it develops everywhere in the body - affecting the heart, brain, visceral and peripheral arteries almost simultaneously or sequentially. Therefore, the detection of prognostic markers that can be applied in the subclinical stage of the atherosclerotic process could identify high-risk patients and optimize prevention and early treatment.

The dissertation is well structured and illustrated. It consists of: 170 pages, illustrated with 90 tables and 19 figures. Includes the following sections: Contents - 3 pages, Abbreviations and symbols used - 2 pages; Introduction and literature review - 21 pages; Purpose and tasks - 1 page; Material and methods - 17 pages; Own results and discussion - 98 pages; Conclusions and recommendations - 3 pages; Bibliography - 19 pages; Appendix - 4 pages. The bibliographic reference contains 208 literary sources, of which 15 in Cyrillic and 193 in Latin.

The literary review is extensive and comprehensive.

The aim of the dissertation is clearly stated: study of the multifocality of atherosclerosis as a pathological process in order to establish and offer prognostic and diagnostic ultrasound markers.

There are 6 propositions:

1. To study the incidence of multifocal atherosclerosis in patients with peripheral atherosclerosis.

2. To determine the clinical characteristics and risk profile of patients with peripheral and multifocal atherosclerosis

3. To study with ultrasound methods the morphological (IMT, plaques, stenoses) changes of the carotid and peripheral arteries (femoral, foot arteries and abdominal aorta) in patients with peripheral atherosclerosis.

4. To determine the relationship between atherosclerotic risk factors and data from ultrasound morphological changes of the carotid and peripheral arteries in patients with multifocal atherosclerosis.

5. To analyze the morphological changes of the carotid, femoral, costal arteries and abdominal aorta and to evaluate as markers and predictors of atherosclerosis.

6. To develop and propose a set of diagnostic and prognostic markers to optimize the screening and diagnosis of multifocal atherosclerosis

Material and methods

The current prospective study includes a total of 240 participants in the age range 32-91 years, admitted to the Clinic of Vascular Surgery at Sofiamed University Hospital in the period from July 2017 to July 2020. All patients included in the study were studied for the presence of risk factors for atherosclerosis (hypertension, diabetes, smoking, alcohol consumption, body mass index, dyslipidemia, familial burden) and experienced revascularization interventions.

Computed tomographic angiography from the renal to the foot arteries, color-coding duplex scanning (CCDS) for morphological changes (intima media thickness - IMT, plaques, stenosis, thrombosis) of the carotid, femoral, foot arteries, diameter of the abdominal aorta and ABI were performed.

Patients were divided into four groups as follows:

Group I - control - patients with risk factors without atherosclerosis. The group includes a total of 40 subjects - 31 men and 9 women aged 32 to 91 years.

Group II - patients with only chronic peripheral arterial disease of the limbs (PAD) - pronounced atherosclerosis in one focal. 127 patients were included: 93 men and 34 women, aged 41 to 88 years, mean age - 67.89 years. The Fontaine Classification was used to assess the degree of PAD. In our study, patients with grade I and grade II of PAD were grouped into a common subgroup.

Group III - this group is divided into two subgroups depending on the scope of the atherosclerotic process, involving two basins simultaneously.

IIIa gr. - patients with PAD and accompanying carotid atherosclerosis. IIIb gr. - patients with PAD and coronary atherosclerosis (CHD).

Group IV - patients with both PAD and CAD and CVD, which covers 35 people and accounts for 16% of all patients

In conditionally named for convenience *group V included 120 patients with PAD (from II, III and IV groups described above), who experienced revascularization of lesions of the arteries of the lower extremities* and are on therapy with statins and fibrates were observed 2 d.

Statistical Methods: Patient data were processed with IBM SPSS Statistics v.23. P <0.05 was chosen as the significance level for all inspections. All conclusions are true with a probability of 95% and the possibility of not being true with a probability of 5%. The most modern methods for analysis of parameters in biostatistics are used.

Results:

As a result of the obtained data, a set of diagnostic and prognostic markers has been developed to optimize the screening and diagnosis of multifocal atherosclerosis. The complex includes:

- Risk factors for multifocal atherosclerosis:
  - Age> 68 years
  - Arterial hypertension
  - Diabetes mellitus
  - Dyslipidemia
  - Obesity (BMI> 27)
  - Smoking
  - Family burden
- Ultrasound diagnostic methods:
  - Great finds
    - Measurement of ABI <0.9
    - Presence of carotid artery stenosis and / or thrombosis
    - Presence of femoral artery stenosis and / or thrombosis
  - Small finds
    - Presence of plaques on carotid arteries
    - Presence of plaques on the femoral arteries
    - IMT of carotid arteries> 1 mm
    - IMT of a common femoral artery> 1 mm
    - Dilatation and aneurysm of the abdominal aorta.

Based on the established results and statistical dependencies, an algorithm for optimizing the diagnosis and therapeutic behavior in patients with multifocal atherosclerosis has been developed, which is of great practical importance.

Conclusions based on the results obtained - 17 in number:

1. A high incidence (55%) of multifocal atherosclerosis has been reported in patients with PAD. Affection in two areas (PAD and CHD /PAD and CVD) is diagnosed in 40.4%, and in three (PAD and CHD and CVD) - in 14.6%.

2. The risk profile of patients for prediction and development of atherosclerotic process is determined by the following factors: male gender, age over 65 years, the presence of AH, diabetes, family history, exercise, dyslipidemia. The risk patient is a middle-aged man of 68 years with PAD, AH, family burden. In the presence of these factors, a risk of developing a multifocal atherosclerotic process is established.

3. The first five risk factors in all patients are family history, hypertension, male gender, smoking and alcohol. For survivors of stroke and AMI, the most important quantitative factors are LDL and HDL, and for patients with high IMT of CA and CFA, age and cholesterol levels.

4. Diabetes mellitus is a risk factor for PAD and its severity and duration are associated with a more advanced stage of vascular involvement.

5. Patients with PAD have pathological structural and functional changes in the following ultrasound parameters: IMT ICAb, IMT ICA, IMT CFA, plaque, stenosis, thrombosis of carotid and femoral arteries, ABI <0.9, as a marker and markers of a multifocal atherosclerotic process.

6. There is an inverse relationship between ABI levels and the likelihood of experiencing stroke - the lower the ABI levels, the higher the likelihood of developing stroke. When the ABI reaches levels of 0.2 then the probability of developing stroke becomes over 50%.

7. In patients with PAD, stenosis of the aoiliac segment is found in almost 1/3 of the patients. Aortic segment thrombosis is diagnosed in just over 1/10. In patients with MSD, thrombosis of the aorto-iliac segment is diagnosed more often (20%) than those without MSB (9.2-9.7%). Aorto-iliac segment thrombosis can be used as a predictor of SMEs.

8. Femoropopliteal segment thrombosis was found in almost half of the studied patients. Stenosis of the femoropopliteal segment bilaterally is found much less frequently. There is a tendency for a higher incidence of femoropopliteal segment thrombosis in patients with coronary heart disease (58.5%) compared to those without (45.2%), as well as in patients with CVD (57.0%) compared to those with without (44.0%). The significant association between femoropopliteal thrombosis and coronary heart disease and / or CVD may be a predictor of multifocal atherosclerosis (CVD and / or coronary heart disease).

9. An important factor in determining the possibility of atherosclerotic process in the cerebrovascular basin in patients with PAD is the statistically significant inversely proportional relationship between IMT CA and ABI - the lower the ABI, the higher the IMT of CA, most often on CCAbif. and ICA.

10. Patients with high levels of ITM are most often men between the ages of 69 and 70 who use alcohol and cigarettes, with an obesity BMI of 26-27, with a family history of hypertension, and with stage III of PAD, with cholesterol levels of 5.60-5.70, triglycerides 1.9-2.0, HDL 1.3-1.4 and LDL 2.9.

11. The established directly proportional relationship between the IMT of CA and FCA with the components of the lipid profile and mainly with the triglycerides - the higher the values of the triglycerides, the more the IMT increases to CCA, CCA bif., ICA, FCA can be successfully used in patient follow-up and for proper assessment of therapy.

12. The analysis confirms that for IMT of CA, a statistically significant pathological difference in IMT levels was found between patients with and without CVD.

13. The established statistically significant relationship between the increase in IMT CA and the presence of clinical / asymptomatic coronary atherosclerosis is defined as an important factor in the prediction of coronary atherosclerosis.

14. The presence of plaque or stenosis of CA increases the relative risk of PAD, CVD or CHD.

15. Higher levels of fibrinogen and pathological lipid profile have been found in more severe atherosclerosis (lower ABI or multifocal involvement). These indicators can be used as markers for the atherosclerotic process.

16. In statin or fibrate treatment, the incidence of adverse events in the CVD group is manageable, reducing the residual risk in patients with atherogenic dyslipidemia and hypertriglyceridaemia.

17. In more aggressive secondary prophylaxis with statins, antiplatelet agents and ACE inhibitors, such as group IV therapy, a reduction in the progression of the atherosclerotic process is found.

We recommend that their number be reduced and summarized.

Contributions (according to the wording in the dissertation) - 7 original and 5 confirmatory:

With original character:

1. Based on an in-depth analysis of the results of clinical, laboratory and instrumental methods of patients with PAD, their risk profile and the prerequisites for screening and prevention have been established.

2. Pathological structural changes in the following ultrasound parameters were found in patients with PAD: IMT ICAb, IMT ICA, IMT FCA, presence of plaques, stenoses, thrombosis of carotid and femoral arteries, ABI <0.9, as a sign and markers of multifocal atherosclerotic process.

3. Structural changes in all arteries (carotid, iliac, femoral, foot) in patients with PAD have been identified as appropriate markers for the detection of multifocal atherosclerosis.

4. The effectiveness of the combined application of ultrasound markers for optimizing the screening and diagnosis of multifocal atherosclerosis has been established.

5. A set of diagnostic and prognostic markers for optimizing the screening and diagnosis of multifocal atherosclerosis is proposed

- IMT over 1 mm, plaques of carotid and / or femoral arteries, stenoses and / or thrombosis of carotid and / or femoral arteries, ABI below 0.9, dilatation and aneurysm of the abdominal aorta.

6. Based on the established results and statistical dependencies, an algorithm has been developed to optimize the diagnosis and therapeutic behavior in patients with multifocal atherosclerosis.

7. The proposed prognostic markers used in the subclinical stage of the atherosclerotic process contribute to the identification of high-risk patients and to the optimization of prevention and early treatment.

Confirmatory:

1. It is confirmed that the classic risk factors for PAD are essential for the development of multifocal atherosclerosis - male, over 68 years of age, hypertension, diabetes, smoking, family history, dyslipidemia.

2. The first morphological changes in the arterial wall can be visualized by B-mode ultrasonography. It is confirmed that this non-invasive method is one of the best for detecting the early stages of atherosclerosis, as it is easy to apply, the equipment is available in many places, and its resolution is better than that of magnetic resonance imaging and CT .

3. It has been proven that the presence of plaque or stenosis of CA contributes to an increased risk of PAD, CVD or CHD in the range of 4-8%.

4. Adverse vascular events have been shown to be manageable with statin or fibrate, reducing the residual risk in patients with atherogenic dyslipidemia and hypertriglyceridemia.

5. More aggressive secondary prophylaxis with statins, antiplatelet agents and ACE inhibitors in high-risk patients contributes to lower progression of the atherosclerotic process.

Contributions can also be summarized in smaller numbers.

Associations with the dissertation: presented with 5 publications, in 3 of which Dr. Gerova is the first author.

Conclusion: The dissertation of Dr. Elitsa Rashkova Gerova - Micic is an in-depth study of multifocal atherosclerosis and diagnostic and prognostic markers in different vascular basins. In the course of the exhibition the doctoral student shows in-depth knowledge of the scientific literature, as well as good opportunities for collecting, analyzing and summarizing the results obtained. I especially appreciate the developed practical algorithm for optimizing the diagnosis and therapeutic behavior in patients with multifocal atherosclerosis. The recommendations do not reduce the value of the proposed dissertation, which fully meets the criteria of the law on the development of the academic staff of the Republic of Bulgaria and the rules of Acibadem City Clinic UMHAT Tokuda EAD for awarding the educational and scientific degree "PhD". That is why I recommend the esteemed members of the scientific jury to vote positively for the award of the educational and scientific degree "PhD" to Dr. Elitsa Rashkova Gerova - Micic

15.06.2022

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