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CLINICAL SIGNIFICANCE OF VARIABILITY OF ATHEROGENIC INDEX OF PLASMA IN PATIENTS WITH LOWER LIMB PERIPHERAL ARTERIAL DISEASE ON LIPID-LOWERING THERAPY

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CLINICAL SIGNIFICANCE OF VARIABILITY OF ATHEROGENIC INDEX OF PLASMA IN PATIENTS WITH lower limb peripheral arterial disease ON lipid-lowering therapy (abstract): Atherosclerosis, as the pathophysiological substrate of lower limb peripheral arterial disease (LLPAD), is a major health problem given the multitude of associated diseases and its severe course. Atherogenic index of plasma (AIP), defined as the logarithmically transformed ratio of concentrations of triglycerides (TG) to HDL-cholesterol is one of the main evaluation parameters of the atherosclerotic process, its variability being an important predictive factor of treatment response. **Aim**: The evaluation of clinical significance of AIP in patients with LLPAD on lipid-lowering therapy with statins and fibrate association. **Material and methods**: Retrospective study of a group of 160 patients aged 40 to 89 years diagnosed with LLPAD and on lipid-lowering treatment with statins and fibrate, hospitalized at the Cardiovascular Rehabilitation Clinic of the Iaşi Rehabilitation Hospital. During the 2 study years (January 1st, 2012-December 31st, 2013), the subjects received daily a constant maximum therapeutic dose of statin and fibrate. Demographic and anthropometric variables were considered and serological parameters were evaluated (total cholesterol-TC, TG, HDL-cholesterol, LDL-cholesterol and AIP) both before and after starting the treatment. In addition, the following symptoms were evaluated on a scale of 0 to 10 at the beginning and at the end of the study: intermittent claudication, feeling of cold feet, paresthesia. **Results and discussion**: There were significant reductions in TC, TG and implicitly in AIP levels. Analysis of clinical response showed that patients who achieved an AIP under 5 (117 cases-73%) experienced a significant reduction of symptoms, associated with a change in disease staging classification; in patients with an AIP over 5 (43 cases-27%) no variations of symptoms were recorded, the previous staging classification remaining unchanged. **Conclusions**: A 2-year constant dose of statin and fibrate combination in patients with LLPAD is associated with a decrease in AIP levels and correlates with symptoms reduction and improvement in the disease staging classification. Thus, an adequate control of lipid profile has beneficial effects on the clinical manifestations of LLPAD. **Keywords**: Atherogenic index of plasma, lipid-lowering therapy, lower limb peripheral arterial disease, atherosclerosis.

Peripheral artery disease (PAD) comprises a multitude of different diseases in terms of etiology and pathogenesis that have in common damage to lower and up-
per extremity arteries (1). This group of diseases includes the chronic peripheral artery disease of lower limbs and its acute form (acute peripheral arterial occlusion), thromboangiitis obliterans (Buerger's disease) and the functional vascular disorders: Raynaud's disease, acrocyanosis, livedo reticularis. Lower Limb Peripheral Arterial Disease (LLPAD) is an obstructive disease that causes progressive narrowing of the lumen and decreased blood flow to the limbs, atherosclerosis being the most common cause (2). The prevalence of arterial occlusive diseases is dependent on age and sex, men over 70 years with multiple cardiovascular risk factors being most commonly affected. The prevalence of PAD in Romania varies directly with age, from 2.5% in the population aged 40-59 years to 18.8% in the population aged 70-79 years (2, 3).

The clinical picture of LLPAD includes a multitude of symptoms, the most important being intermittent claudication, paresthesia and cold feet. Of these, intermittent claudication is the key element in Leriche-Fontaine classification, as follows: stage I-asymptomatic; stage IIA -intermittent claudication after more than 200 meters of walking; stage IIB-intermittent claudication after less than 200 meters of walking; stage III-rest pain; stage IV-ischemic lesions: ulcers, gangrene, necrosis (4, 5, 6).

Atherogenic index of plasma, defined as the logarithm of the ratio between the concentration of triglycerides (TG) and HDL-cholesterol is one of the main benchmarks of the atherosclerotic process and hence of LLPAD, the variability of which is an important factor of predictability of treatment response (7, 8).

MATERIAL AND METHODS
A single-center, observational, descriptive and retrospective study was conducted on a sample of 160 subjects aged 40 to 89 years, hospitalized at the Cardiovascular Rehabilitation Clinic of Iasi Rehabilitation Hospital between January 1st, 2012 and December 31st, 2013. Inclusion criteria for the study were: LLPAD stage II (A or B) or III, a baseline TG level of more than 150 mg/dL, TC level over 220 mg/dL and HDL cholesterol under 35 mg/dL, absence of lipid-lowering therapy at study initiation. Exclusion criteria were: LLPAD stage I or IV, normal TG level, HDL-cholesterol level over 35 mg/dL and TC under 220 mg/dL, lipid-lowering medication. During the 2 years of study, the subjects received constant daily maximum therapeutic dose of statin and fibrate. Demographic variables, anthropometric and serological parameters (TC, TG, HDL-cholesterol, LDL-cholesterol, AIP) were assessed both before and after starting treatment. The following symptoms have also been evaluated on a scale of 0 to 10: intermittent claudication, cold feet, paresthesia, both at the beginning and end of the study.

The obtained data have been processed using SPSS 21.0 (SPSS, Inc., Chicago, IL, USA).

RESULTS
After clinical examination, the patients included in the study were stratified according to Leriche-Fontaine classification as follows: stage IIA-20 (12.5%) patients, stage IIB-67 (41.6%) patients, stage III-73 (26.8%) patients (fig. 1).

At the end of the two years of study, after a constant daily maximum dose of statin and fibrate, the distribution of patients according to disease stage was: stage IIA-107 (66.8%) patients, stage IIB-40 (25 %) patients, and stage III-13 (21.6%) patients (fig. 2).
The data obtained and illustrated in the above figures show that, as a result of the treatment administered during the two-year study, 30 patients (18.7%), previously staged as stage III, were reassigned as stage II, while 87 patients (54.3%), previously staged as stage IIB, were reassigned as stage IIA.

As mentioned above, every symptom present on admission (paresthesia, intermittent claudication and cold feet) were evaluated on a scale of 0 to 10, with 0 meaning the absence of symptom and 10 the highest intensity. During the study, revaluations were performed every 6 months, significant improvements in the grades of the patient being recorded (fig. 3).

Thus, a total of 110 patients (68.7%) showed an improvement by least two points on the pain scale (fig. 4).

Regarding AIP, at the end of the two-year study a significant number of patients (117/73%) had a decrease in value below 5, while in a smaller percentage (43/27%) the value remained above 5 (fig. 5).
**DISCUSSION**

The process of atherosclerotic lesion formation is slow and remains asymptomatic until lumen compromise or vascular occlusion (9, 10). The pathophysiological processes involved are enhanced as well by classical risk factors for developing PAD: cigarette smoking, hypertension, diabetes and hyperlipidemia (11). Lipid abnormalities are known to have a critical role in the development of atherosclerosis, so that the administration of lipid-lowering medication has beneficial role both in preventing the occurrence of atherosclerotic lesions and in slowing the pathophysiological processes, with default improving of symptoms (12, 13).

Although the main goal of lipid-lowering therapy is to reduce the LDL-cholesterol levels, it is well known that high levels of TG and TG-rich lipoproteins (TRLs) are a cardiovascular risk factor.
(14). On the other hand, hypertriglyceridemia is associated with low HDL-cholesterol levels; thus, although the lipid-lowering therapy is not targeted at correcting the HDL level, it is used to reduce hypertriglyceridemia (15). In the literature, there are case reports of patients with normal TG levels associated with low HDL-cholesterol (16, 17, 18). Due to the fact that HDL-cholesterol level is a marker of cardiovascular risk, uncorrelated with the atherogenic process, its isolated correction is not associated with a decreased risk (19). Recent studies have shown that aggressive treatment with lipid-lowering agents (maximum therapeutic dose) is associated with better prevention of cardiovascular events (20).

**CONCLUSIONS**

The present study demonstrates the efficacy of lipid-lowering therapy with statin and fibrate in constant maximum therapeutic doses administered for 2 years in patients with stage II and III LLPAD. Thus, there was a significant reduction of symptoms associated with improvement in disease staging, through the improvement of the lipid profile and therefore a decrease in AIP.

**REFERENCES**

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**NEWS**

**NEW PROTECTIVE ROLE OF IL-22 IN MYCOBACTERIUM TUBERCULOSIS INFECTIONS**

In a study by Treerat *et al.*, the functional role of IL-22 pathway in immunity against *Mycobacterium tuberculosis* strains was assessed. A member of the IL-10 cytokine family, IL-22 has both protective and pathological functions on mucosal surfaces. The study used as a prototype *M. tuberculosis* HN878, a member of the W-Beijing lineage and showed that the microorganism stimulates IL-22 production, using a TLR2 dependent mechanism. The study showed that IL-22 mediates protective immunity in chronic stages of infection in mice and that IL-22-dependent pathway in macrophages and epithelial cells mediate protective mechanisms for infection control (Treerat P, Prince O, Cruz-Lagunas A, Muñoz-Torrico M, Salazar-Lezama MA, Selman M, *et al.* Novel role for IL-22 in protection during chronic *Mycobacterium tuberculosis* HN878 infection. Mucosal Immunol. 2017 Mar 1. doi: 10.1038/mi.2017.15.)

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