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Short report

Cardiovascular Disease Continuum – Peripheral Artery Disease Versus Coronary Heart Disease

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ABSTRACT

Peripheral artery disease (PAD) is an occlusive disease of extremities, which used to be diagnosed and treated as an isolated disease of the limbs or other parts of the body. Nowadays, the role of PAD transcends the affected limb; instead, the cardiovascular system must be observed as a whole, with PAD having a prognostic role. About 200 million people are affected by PAD worldwide. The prevalence of PAD is likely to increase steadily in the future due to the global aging of the population and the predominantly sedentary lifestyle, along with the expected universal increase in the major PAD risk factors such as smoking habit, diabetes mellitus, dyslipidemia and hypertension. Patients with PAD are at a higher risk of coronary disease and cardiovascular events in comparison to healthy control subjects. The severity of PAD correlates with the development and complications of cardiovascular disease. In PAD patients, percutaneous coronary intervention is more demanding, associated with more comorbidities, more complex lesions, and poorer procedural success as compared with PAD-free patients. For a year now, the use of antiplatelet therapy with acetylsalicylic acid in combination with low (vascular) dose of a direct oral anticoagulant has been recommended for cardiovascular and lower limb protection in PAD patients. In the future, we expect a better understanding of atherosclerotic disease, stronger modulation of systemic inflammation, and the discovery of new therapies. In the meantime, it is necessary to identify the risk population and aggressively treat the classic factors – control of blood pressure, glycemia and lipids with antiplatelet and new anticoagulant therapy. The goal is to protect the limb and preserve the cardiovascular continuum. The negative consequences of COVID-19 on treatment CVD will be estimated in the following years.

Key words: *cardiovascular disease, peripheral artery disease, atherosclerosis, risk factors, coronary, lower extremity, primary prevention*

Introduction

Cardiovascular diseases (CVDs) are the leading cause of disability and premature death in the world[1]. According to the Global Burden of Disease Study, 422.7 million people were affected with CVD and 17.9 million deaths were caused by CVD, accounting for 31% of all-cause deaths in the world in 2015[2]. CVDs impose a huge and ever growing burden upon the individuals, families, and healthcare system, obviously necessitating urgent and effective research of atherosclerotic pathophysiology and implementation of preventive measures[3,4]. The main clinical manifestations of CVD can be divided into those involving the heart and cardiovascular system (coronary/ischemic disease); brain and cerebrovascular system (cerebrovascular disease); and lower extremities (occlusive disease of peripheral arteries)[5]. Most frequently, atherosclerosis underlies all these diseases. Atherosclerosis is a progressive condition characterized by diseased endothelium, low-grade inflammation, lipid accumulation, and plaque formation within the vascular wall intima media[6]. Plaque rupture or erosion can cause superimposed atherothrombosis and subsequent vascular occlusion, which in turn leads to cardiovascular events including myocardial infarction, stroke, limb ischemia, and cardiovascular death[7]. In Europe, about 4 million people die from CVD *per* year, accounting

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for 45% of all-cause deahs[8]. More than 42% of coronary disease patients also suffer from peripheral artery disease[9].

Peripheral Artery Disease Definition and Diagnosis

Peripheral artery disease (PAD) defines an atherosclerotic stenosis or occlusive disease involving the arteries of upper and lower extremities, arteries of the cerebrovascular system (carotid and vertebral arteries), mesenteric and renal arteries, but not including aorta and coronary artery disease. Polyvascular disease is a specific entity defined as concomitant existence of clinically relevant atherosclerotic disease in at least two large vascular territories. Patients with lower extremity and carotid artery PAD have a high risk of associated coronary artery disease (CAD), therefore requiring interdisciplinary approach in diagnosis and treatment[10]. This article will primarily tackle atherosclerotic events in lower extremities. Lower extremity PAD can be asymptomatic or accompanied by symptoms such as intermittent claudication, atypical pain in legs, critical limb ischemia, and occasional acute limb ischemia[11]. Irrespective of the presence of symptoms, PAD is associated with a significantly higher risk of CVD morbidity and mortality, thus posing a major public health problem[12]. Atherosclerosis is the most common cause of PAD, which makes it a primary therapeutic target[13]. The process of PAD diagnosis includes patient history data, clinical or physical examination, and subclinical identification of peripheral atherosclerotic disease by use of noninvasive diagnostic methods. The basic diagnostic test is determination of the ankle-brachial index (ABI) used not only to confirm the diagnosis but also to determine PAD severity. The values of ABI <0.9 are considered as pathologic, whereas ABI <0.5 indicates a high risk of amputation[14]. This can be followed by computed tomography angiography (CTA) and digital subtraction angiography (DSA), which is currently employed when endovascular intervention is planned[15]. Contrast magnetic resonance angiography (MRA) has higher specificity than CTA and higher sensitivity than duplex US in detecting >50% arterial stenosis, and is better tolerated by patients as compared with contrast angiography.

Association of Peripheral Artery Disease and Coronary Disease

Patients with PAD are at a higher risk of subclinical coronary disease and cardiovascular events as compared with healthy control subjects[16]. Cardiovascular risk correlates with symptom severity. Hospitalization for symptomatic PAD is a potential marker of the disease severity and is associated with poorer outcomes[17]. Symptomatic PAD is associated with 70% greater risk of cardiovascular events and 80% greater risk of death as compared with PAD-free patients. The prevalence of myocardial infarction is 2.5-fold greater in patients with clinically significant PAD (defined as ABI <0.9) as compared with PAD-free patients[18]. Recent studies have revealed that local indicators of peripheral artery atherosclerosis other than ABI value, e.g., plaque echogenicity or femoral artery intima-media thickness (IMT), also are useful parameters in cardiovascular risk assessment[19,20]. The presence of PAD is frequently associated with advanced coronary disease, including involvement of the main coronary trunk or polyvascular coronary disease quantified by a high SYNergy between percutaneous coronary intervention with TAXus and cardiac surgery (SYNTAX) study result. The severity of PAD correlates with the cardiovascular disease development and complications. The mechanism underlying these observations most probably is multifactorial[21]. PAD patients having undergone chronic total occlusion percutaneous coronary intervention (CTO PCI) had more comorbidities, more complex lesions, and poorer procedural success as compared with PAD-free patients[22]. The cross-talk of PAD, CAD and cardiovascular events can be defined as clinical overlapping with the established atherosclerotic risk factors that predict development of both PAD and CAD. Among others, these risk factors include male sex, age, diabetes mellitus, smoking habit, hypertension, hyperlipidemia, and chronic renal failure. In addition to the traditional risk factors, first-degree relatives of PAD patients are exposed to a higher risk of subsequent development of PAD and cardiovascular events, thus emphasizing the hereditary nature and multifactorial contribution to the disease onset[23]. Upon recognizing the clinical or subclinical manifestations of PAD, the effect of atherosclerotic disease can be alleviated by aggressive modification of the risk factors. The increasing rate of adverse cardiovascular events in PAD patients may in part be attributed to the less aggressive management of those risk factors. It is known that peripheral vascular disease is quite frequently under-recognized and under-treated in these patients. Patients with concomitant PAD and CAD are prescribed more sparing antiaggregating therapy, beta-blockers, angiotensin-converting enzyme (ACE) inhibitors and statins as compared to patients with coronary disease alone. It has been demonstrated that higher statin doses and lower low-density lipoprotein cholesterol (LDL-C) levels are independently associated with better outcomes in these patients, suggesting the value of therapy targeted to risk factors, particularly considering the lack of alternative treatment strategies[24]. It can be speculated that PAD actually is a peripheral manifestation of the already existing coronary disease, for which such preventive measures could prove useful. Besides the overlapping risk factors, PAD can independently trigger unfavorable cardiovascular events. Phenotypic variations in the risk factor profiles have been observed between patients with peripheral and coronary disease. PAD patients tend to have higher triglyceride and high-density lipoprotein cholesterol (HDL-C) levels. In addition, PAD causes functional restrictions in exercise or in the activities known to be cardioprotective. Furthermore, PAD

patients are known to have abnormal peripheral vasodilation and paradoxical vasoconstriction in response to the increased metabolic demands induced by stress[25]. This inadequate arterial vasodilation can lead to enhanced systemic load, thus reducing heart action and oxygen supply. This mechanism contributes to unfavorable cardiovascular outcomes. The higher prevalence of adverse cardiovascular events in PAD patients most likely results from a combination of overlapping direct and indirect causative factors associated with the development of PAD and its hemodynamic sequels. Inflammatory markers (C-reactive protein /CRP/, fibrinogen, interleukin-6, tumor necrosis factor-α) have also been identified as one of the strongest predictors of cardiovascular risk in patients with PAD and coronary disease. A novel therapeutic goal will be identifying the triggers of inflammation in the development of atherosclerotic disease and modulation of inflammation in PAD and CAD.

Treatment of Peripheral Artery Disease

The aim of PAD management is to improve the patient quality of life, to increase walk distance, and to reduce the prevalence of fatal cardiovascular events[26]. PAD and CVD show overlapping conditions of similar yet separate basic pathophysiologic mechanisms. The severity of PAD correlates with cardiovascular outcomes. With the ever better and refined understanding of atherosclerotic disease, modulation of systemic inflammation will play ever more important role in upgrading therapeutic options for both diseases. Until then, the latest guidelines for PAD management are focused on aggressive modification of risk factors, smoking cessation, introducing antiaggregation therapy, hypolipemics, optimal glycemia and blood pressure regulation in PAD patients, with the highest level of recommendations addressing symptomatic patients, and walking exercise[26]. In patients with artery stenosis >80%, recommendations include organized exercises to increase walk distance at least three times a week for at least 12 weeks in the form of 45- to 60-min training. According to the Evidence-based Practice Center Systematic Review Protocol, the majority of studies report on the increase in walk distance to occur after 6 months to 2 years of exercise. In addition, increasing walk distance is efficiently supported by medicamentous therapy for PAD, especially cilostazol and naftidrofuryl. Cilostazol improves arterial blood flow to lower extremities *via* two mechanisms, i.e. by preventing thrombus formation and vasodilation. However, the main side effects of this agent are headache and diarrhea, while it is contraindicated in patients with heart failure. Naftidrofuryl reduces platelet and red blood cell aggregation, and according to a meta-analysis of five studies, it is efficient in reducing pain and increasing walk distance by 26% as compared with placebo[27]. The use of ACE inhibitors and angiotensin receptor antagonists in patients with hypertension and PAD is associated with a decreased rate of major cardiovascular events and mortality, thus they should be the preferred treatment option[28,29]. In patients with mild to moderate limb ischemia, therapy with beta-blockers did not aggravate disease symptoms; however, caution is warranted in patients with critical limb ischemia[30]. Antiplatelet therapy is indicated for secondary prevention of cardiovascular events in patients with symptomatic PAD. Standard antiplatelet therapy for PAD includes use of monotherapy in all patients with carotid artery stenosis, irrespective of clinical symptoms and revascularization; monotherapy in case of symptomatic disease of lower extremity arteries, where clopidogrel is preferred over acetylsalicylic acid; dual antiplatelet therapy for at least one month of percutaneous revascularization of lower extremities; and permanent oral anticoagulant therapy in combination with antiplatelet therapy for at least one month of percutaneous revascularization in patients with PAD and atrial fibrillation and with CHA2DS2-VASc score ≥2 or after implantation of mechanical cardiac valve[31]. After COMPASS study, antiplatelet monotherapy with acetylsalicylic acid in combination with low (vascular) dose of rivaroxaban, a direct oral anticoagulant (2.5 mg twice daily), is recommended for better cardiovascular and lower limb protection in PAD patients[32,33]. Results of the VOYAR PAD study published in March 2020 showed the use of the same (vascular) dose of rivaroxaban in combination with acetylsalicylic acid to be superior to acetylsalicylic acid monotherapy in PAD patients having undergone lower extremity revascularization, those with a significantly lower prevalence of composite outcome of acute limb ischemia, major amputation due to vascular causes, myocardial infarction, ischemic stroke, or death from cardiovascular causes. The incidence of thrombolysis in myocardial infarction (TIMI) major bleeding did not differ significantly between the groups. The incidence of major bleeding according to the International Society on Thrombosis and Hemostasis (ISTH) was significantly greater with a combination of rivaroxaban and acetylsalicylic acid than with acetylsalicylic acid alone[34]. In patients with symptomatic intermittent claudication, revascularization was indicated after failure of optimal medicamentous therapy and exercise therapy. In this patient population, the aim of revascularization is to improve their functional status and quality of life, and to prevent critical limb ischemia. Endovascular approach is recommended in patients with claudications that restrict their quality of life, with hemodynamically pronounced aortoiliac disease, primarily in case of femoropopliteal occlusion <25 cm, whereas surgical revascularization is the preferred option in others. Extremity amputation is the method of choice in patients with irreversible lower limb ischemia and in those with extensive necrosis or infected gangrene[35]. Critical limb ischemia is associated with 20% higher mortality and 50% greater risk of extremity amputation in patients not submitted to approach, tailored to each individual patient, including due control of atherosclerotic risk factors, revascularization, and rehabilitation protocol.

Impact of COVID–19 on Peripheral Artery Disease

Morbidity and mortality associated with PAD increased significantly during the COVID-19 pandemic[37]. Bellosta et al. observed an increased incidence of acute limb ischemia in patients with COVID-19 infections and an almost eightfold increase in total patients with acute limb ischemia during peak COVID-19 pandemic compared to the same time period 2019[38].

COVID-19 infection can cause severe alterations in coagulation mechanisms, leading some patients to present severe acute arterial complications such as thrombosis, as the only associated manifestation[39]. During the COVID-19 pandemic the organization of work of health institutions has significantly changed and focused attention on pandemic management. This has led to important changes in the treatment of patients without COVID-19 and resulted in heavier approach to care with delayed diagnosis and treatment. All recommendations for treatment PAD stem from the time before the COVID-19 pandemic. The COVID-19 pandemic has had repercussions for patients with peripheral artery disease that range from increased amputations to payoffs in terms of efforts to keep patients out of hospitals while still complying to treatment recommendations. The real consequences of COVID-19 on treatment CVD will be estimated in the following years.

Conclusion

PAD is an important indicator of overall cardiovascular health due to its underlying pathophysiology – atherosclerosis. The prevalence of PAD is likely to increase steadily in the future due to the global aging of the population and the predominantly sedentary lifestyle, along with the expected universal increase in the major PAD risk factors such as smoking habit, diabetes mellitus, and hypertension.

The goal is to diagnose asymptomatic PAD as early as possible because it is a sign of systemic atherosclerosis. A strong correlation between symptomatic PAD and the severity of cardiovascular outcomes was confirmed. Therefore, it is of utmost importance to identify the population at risk, to influence the occurrence of the disease by appropriate primary prevention measures, and to modify risk factors by lifestyle modification and therapeutic measures available. The main goal of current therapy is better cardiovascular and lower limb protection in PAD patients. We believe that novel therapy will be focused on timely recognizing the triggers of inflammation in atherosclerotic disease development, along with modulation of inflammation in PAD and CAD. The COVID-19 pandemic also has had repercussions for patients with peripheral artery disease that range from increased amputations to payoffs in terms of efforts to keep patients out of hospitals while still complying to treatment recommendations. Further follow-up is still needed for the long-term outcomes of the COVID-19 pandemic on the treatment of CAD.

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BOLESTI KARDIOVASKULARNOG KONTINUUMA – PERIFERNA ARTERIJSKA BOLEST PREMA KORONARNOJ BOLESTI

S A Ž E T A K

Bolest perifernih arterija (PAD) okluzivna je bolest ekstremiteta koja se nekad dijagnosticirala i liječila kao izolirana bolest udova ili drugih dijelova tijela. U današnje vrijeme uloga PAD-a prevladava zahvaćeni ud; umjesto toga, kardiovaskularni sustav mora se promatrati u cjelini, pri čemu PAD ima prognostičku ulogu. Oko 200 milijuna ljudi pogođeno je PAD-om širom svijeta. Prevalencija PAD-a vjerojatno će se kontinuirano povećavati u budućnosti zbog globalnog starenja stanovništva i pretežno sjedilačkog načina života, zajedno s očekivanim sveopćim porastom glavnih čimbenika rizika od PAD-a kao što su navika pušenja, dijabetes melitus i hipertenzija. Pacijenti s PAD-om imaju veći rizik od koronarne bolesti i kardiovaskularnih događaja u usporedbi sa zdravim kontrolnim ispitanicima. Ozbiljnost PAD-a korelira s razvojem i komplikacijama kardiovaskularnih bolesti. U bolesnika s PAD-om perkutana koronarna intervencija zahtjevnija je, povezana s više komorbiditeta, složenijim lezijama i lošijim proceduralnim uspjehom u usporedbi s pacijentima bez PAD-a. Već godinu dana preporučuje se primjena antitrombocitne terapije acetilsalicilnom kiselinom u kombinaciji s niskom (vaskularnom) dozom izravnog oralnog antikoagulanta za zaštitu kardiovaskularnih i donjih udova kod bolesnika s PAD-om. U budućnosti očekujemo bolje razumijevanje aterosklerotske bolesti, jaču modulaciju sistemske upale i otkriće novih terapija. U međuvremenu je potrebno identificirati rizičnu populaciju i agresivno tretirati klasične čimbenike - kontrolu krvnog tlaka, glikemije i lipida s antitrombocitima i novu antikoagulantnu terapiju. Cilj je zaštititi ud i sačuvati kardiovaskularni kontinuum. Negativne posljedice COVID-19 na liječenje KVB procijenit će se u sljedećim godinama.