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Review

Common features of atherosclerosis and venous disease

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ABSTRACT

Atherosclerosis and venous diseases exert substantial burden on human population including high prevalence and incidence of mortality and disabling morbidity caused by these disorders. In contrast to the traditional belief, current evidence based on physiological and epidemiological findings indicates that atherosclerotic and venous disease share many common features. Pathophysiological mechanisms underlying both diseases is immune system represented by monocytes/macrophages which interact with endothelial layer of arteries and veins and cause atherosclerotic process and venous insufficiency. From epidemiological point of view, both diseases also share manageable risk factors including obesity, dyslipidemia, and hypertension. In addition, there is evidence for significant and causal association between atherosclerosis and venous thrombosis. Several management strategies including pharmacoherapy are proposed to be effective for prevention and treatment of atherosclerosis and venous disease. However, detailed knowledge of the pathophysiology connecting atherosclerosis and venous disease is still incomplete including data regarding "complex" treatment. The aim of this review is to present available evidence of pathophysiological and epidemiological aspects in common mechanisms of atherosclerotic and venous disease and to summarize clinical implications based on current knowledge.

Contents

1. Introduction

Physician William Harvey (1578–1657) first reliably described structures of the blood circulation. He clearly differentiated arterial and venous systems and correctly predicted their communication by proposing existence of capillaries, the latter later confirmed by Marcello Malpighi (1628–1694), who was already using microscope. Arterial and venous disease since that time have traditionally been regarded as separate entities with different causes and with different predisposing risk factors. In contrast to this traditional and common belief, current evidence based on physiological and epidemiological findings indicates that arterial and venous disease share many identical features.

Arterial and venous disease exert substantial disease burden on human society including mortality and disabling morbidity. At the same time, both entities are to a great extent preventable, sometimes by very similar and rather simple and affordable means. However, this topic is not by far solved and lot of controversies still remain because of our incomplete knowledge of the relevant pathophysiology connecting arterial and venous disease. The aim of this review is to present currently available evidence available in the field of pathophysiology and epidemiology regarding common

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mechanisms of atherosclerosis and venous disease and to summarize clinical implications based on current knowledge in this field.

2. Pathophysiology

Proposed common feature for arterial and venous disease is an inflammatory process in the vessel wall. This process is accomplished by immune system represented by activated monocytes, macrophages which enter subintimal vessel space and initiate damage of the artery or venous wall causing atherosclerosis or dysfunction of venous structures, mainly valves. In the case of atherosclerosis, the most common initiating mechanism is the abundance of LDL particles and their modification in the artery wall [1]. In the case of chronic venous disease the mechanism proposed by majority of experts is venous hypertension [2,3]; some hypotheses list also dyslipidemias as an important cause for venous disease, especially thromboembolic disease [4].

Recent findings also propose additional common pathophysiological/immune mechanisms associated with arterial and venous disease. This mechanism is represented by oxidized low-density lipoprotein/β2-glycoprotein I (oxLDL/β2GPI) complexes which have been implicated in the initiation and progression of atherosclerosis and associated also with idiopathic venous disease. In this study focused on anti-oxLDL/β2GPI antibodies and oxLDL/β2GPI complexes in patients with arterial and idiopathic venous disease in inhibitors of 3-hydroxy 3 methyl glutaryl coenzyme A reductase (statin) naïve patients it was found that patients with arterial and venous disease expressed higher levels of IgG anti-oxLDL/β2GPI antibodies than in healthy controls and that oxLDL/β2GPI complexes were also significantly higher in both groups of patients compared to controls. In addition, multivariate regression analysis indicated that male sex, high cholesterol, and carotid disease were significant indicators for higher oxLDL/β2GPI [5]. The coexistence of oxLDL/β2GPI in arterial and venous disease might actually suggest a common oxidative mechanism for an arterial and venous disease with activation of immune processes mentioned earlier. Because of relatively small number (tens) of participants, results of this otherwise interesting study should be confirmed in larger prospective studies.

Regarding genetic studies, it was also proposed that tumor necrosis factor superfamily, member 4 (TNFSF4) gene could be associated with myocardial infarction and also with venous disorders especially in women. It was shown, that there was significant association of $-921C > T$ variation of this gene with an increased risk of venous thromboembolism in women. Furthermore, using a haplotype-based regression analysis, haplotype C-G was associated with a reduced risk of venous thromboembolism relative to the referent haplotype, C-A. On the contrary, no robust evidence was found for an association of the variants/haplotypes with risk of venous thromboembolism in men or with cardiovascular risk in women. This indicates that in different populations with different representation of men and women different results are to be expected regarding predisposing factors to arterial and venous disease [6].

Another factor under intensive investigation both in arterial/atherosclerotic and venous disease are circulating microparticles (MPs) which are vesicular structures produced by apoptotic and activated endothelial cells but also by other cells associated with circulatory system. Elevated levels of MPS were described both in arterial and venous disorders [7]. However, when MPs levels were compared with those of controls possessing cardiovascular risk factors no significant differences were observed. Therefore, the presence of cardiovascular and venous disease risk factors must be adjusted in conditions accompanied by elevated circulating MPs.

In addition to association between atherosclerosis and chronic venous disease, an association between atherosclerosis and spontaneous or provoked venous thrombosis has been repeatedly reported suggesting that also these two diseases share common risk factors. Supportive evidence comes from several studies that showed that cardiovascular risk is significantly associated with venous thromboembolism [8–10]. On the other hand in other reports, no association was found [11–15]. Nevertheless, in large metaanalysis of case-control and cohort studies with a total of 63,552 patients, cardiovascular risk factors were associated with venous thromboembolism [16]. From pathophysiological point of view there is really evidence supporting biologically plausible explanation that atherosclerosis could have also distant prothrombotic effect. Atherosclerosis is associated with activation of platelets and factors of blood coagulation, it is also associated with increased fibrin turnover; all these factors could at least facilitate thrombotic complications. In the case of atherosclerotic disease, the thrombus formation and emboli very probably are preceded by development of unstable forms of atherosclerotic plaques accompanied by serious endothelial dysfunction. In the case of venous thromboembolic disease the situation is much less clear and in almost half of cases the cause could not be reliably indentified. Common mechanisms for both complications are recently investigated also on the molecular [17-19] and on the clinical [20,21] level.

3. Epidemiology

On the population level, cardiovascular disease, venous disease and thrombotic complications exert extremely high disease burden. The extent of burden of cardiovascular disease was already summarized [22]. Very similar data are now available regarding the global disease burden due to venous thromboembolism, when annual incidences ranging from 0.75 to 2.69 per 1000 individuals in the population were observed [23]. The incidence increased to between 2 and 7 per 1000 among those 70 years of age or more. This burden is primarily based on the incidence of venous thromboembolic events, and to a lesser extent on the estimated number of deaths. The global incidence of venous thromboembolism is especially pronounced in the elderly. This finding has major implications for global health because life expectancy continues to improve in low- and middle-income countries. It is also likely that the high incidence of venous thromboembolism in the elderly reflects the high prevalence of comorbid-acquired risk factors in these patients, especially malignancy, heart failure, and immobility associated with surgery or hospitalization for medical illness, which account for the majority of the population attributable risk in older individuals. Despite treatment, approximately 10–20% of patients with thromboembolic disease develop severe postthrombotic syndrome, a chronic disorder that decreases quality of life and substantially reduces the quality of life. In the most severe cases, patients with postthrombotic syndrome can develop venous ulcers, which heal slowly and their treatment is costly.

In addition, in substantial proportion of affected persons both atherosclerotic and venous diseases occur concomitantly. One of epidemiological studies focused on the association between atherosclerotic changes and chronic venous insufficiency is our Prague pre- and post-menopausal Female Study (3PMFs) in which we analyzed ankle brachial index and subjective signs of chronic venous insufficiency in the 5% representative population sample of more than 900 women from Prague [24]. In this study in women with signs of chronic venous insufficiency we observed significantly higher prevalence of pathological values of ankle brachial index (less than 0.91). In addition, in this study we found that