Diabetes, renal dysfunction, inflammation, and anemia: the deadly quartet in peripheral artery disease

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Abstract

The article reviews the burden of peripheral artery disease (PAD) and its association with diabetes, renal dysfunction, inflammation, and anemia. PAD is a marker of advanced atherosclerotic disease and is associated with a poor quality of life, ischemic events, and mortality. Polyvascular involvement is often observed in PAD patients (pts), and contributes to the greater risk of all-cause and cardiovascular mortality. Diabetes is a major risk factor for PAD, and the presence of PAD in diabetic pts is associated with unfavorable cardiovascular outcomes. In comparison to nondiabetic PAD pts, diabetic pts often have severe forms of PAD such as foot ulcers and gangrene, and more often have involvement of the distal extremities. Diabetes is often accompanied by anemia, particularly in the presence of impaired renal function. Chronic kidney disease and PAD share some common risk factors and frequently coexist. In PAD pts, renal dysfunction has been associated with an increased risk of major adverse cardiovascular events and mortality. Anemia is quite prevalent in PAD pts, especially in those with critical limb ischemia. The severity of anemia has been identified as an independent predictor of limb loss and mortality. C-reactive protein (CRP) is associated with the development of PAD and diabetes. Increased levels of CRP in diabetic pts intensify the risk for PAD development. Data regarding the prognostic role of CRP in PAD pts suggest that CRP is a better prognostic marker for short-term rather than long-term mortality. Considering the close relationship between diabetes, renal dysfunction, inflammation, and anemia in PAD pts, a multidisciplinary approach is needed in order to improve quality of life and prevent ischemic events and fatal outcomes.

Key words: peripheral artery disease, diabetes, renal function, inflammation, C-reactive protein, anemia, mortality
Peripheral artery disease (PAD) is one of the most severe manifestations of atherosclerosis and together with coronary artery disease (CAD) and cerebrovascular (CVD) disease is responsible for more than 1.9 million deaths in the European Union each year [1]. Epidemiological studies have identified PAD as an independent predictor of cardiovascular (CV) mortality [2,3]. The frequent coexistence of CAD and/or CVD in PAD patients (pts) is well assessed [4]. In The REduction of Atherothrombosis for Continued Health (REACH) Registry polyvascular involvement was observed in more than one half of PAD pts, and 70% of polyvascular pts had PAD [5]. The presence of polyvascular disease in PAD pts is independently associated with an increased risk for all-cause and CV mortality [6]. Diabetic pts have a reduced life expectancy of 5-10 years mainly due to premature cardiovascular disease [7]. PAD is common among diabetic pts and predicts CV mortality [8]. Diabetes mellitus is strongly associated with the development of PAD, and higher mortality rates are observed in diabetic PAD pts when compared to nondiabetics [9-11]. Pts with chronic kidney disease (CKD) are more likely to develop PAD compared to individuals with preserved renal function. In pts with CKD, PAD is associated with an increased risk of future ischemic events and mortality [12]. Inflammation and anemia commonly coexist with PAD and CKD, and are associated with unfavorable outcomes [13,14]. Therefore, due to their interrelated pathophysiology, we aimed to review the impact of diabetes, renal dysfunction, inflammation, and anemia on cardiovascular mortality in PAD pts.

2. Epidemiology and clinical characteristics of PAD

In 2010, 202 million people were living with PAD worldwide [15]. The prevalence of PAD rose globally in the past decade, and future growth is expected [2,15]. Considering the decreasing trend of smoking globally, age and diabetes have become the two most important risk factors for PAD [2,16]. According to the National Health and Nutrition Examination Survey, the prevalence of PAD increased by 1% in the 40-49 age group, and to 22.4% in pts older than 80 years [17]. The Hoorn study showed PAD prevalence from 7% in pts with normal glucose tolerance to 9.5% in pts with impaired glucose tolerance, and up to 20.9% in diabetic pts [18]. In the German Epidemiological Trial on Ankle brachial Index which included primary care pts aged 65 years and older, the prevalence of PAD, defined by ankle brachial index (ABI), was higher in pts with diabetes compared to nondiabetic pts (26.3% vs 15.3%, respectively) [19]. A typical symptom of PAD is intermittent claudication, described as cramping or pain in the calves, thighs, or buttocks with exertion, which remits at rest [2]. In diabetic pts, PAD is usually symmetrical and multi-segmental and involves arteries below the knee [20]. Moreover, the arterial walls are often calcified and occlusions are more frequent than stenosis [21]. PAD progression, defined as ABI decline >0.15 is significantly associated with both all-cause and CV mortality [22]. Critical limb ischemia (CLI) is the most severe form of PAD, and 2-3% of pts present with rest pain, ulcer or gangrene [23]. The annual mortality rate in pts with CLI is approximately 25% and between 50-70% at 5 years [24]. Pts presenting with CLI and diabetes more often show progression to gangrene, the limb salvage rate is lower, and the results of revascularization are worse compared to nondiabetics [25].

3. Diabetes and PAD

The International Diabetes Federation estimated that 415 million people aged 20-79 have diabetes worldwide, and projected the increase to 642 million by 2040 [26]. The increasing rate of diabetes has implications for both the prevalence and prognosis of PAD [27]. In diabetic pts, PAD occurs at an earlier age and progresses more rapidly compared to nondiabetics [28]. The extent of PAD is dependent on the duration of diabetes, with longer durations associated with a higher risk of amputations and mortality [20]. Kallio et al. found that after a mean follow-up of 11 years, 21 out of 89 pts (24%) with type 2 diabetes developed PAD. Furthermore, an excess mortality was found in diabetic PAD pts compared to diabetics without PAD (58 vs16%, respectively) [29]. Results from the United Kingdom Prospective Diabetes Study reported a graded and an independent association between hyperglycemia and PAD with each 1% (11 mmol) increase in HbA1c, resulting in a 28% increased risk of PAD [30]. In The Atherosclerosis Risk in Communities study which assessed the relationship between HbA1c and PAD risk in 1894 pts with diabetes, diabetics with poor glucose control (HbA1c>7.5%) were five times more likely to develop intermittent claudication and five times more likely to be hospitalized for PAD compared with diabetics with good glycemic control (HbA1c<6.0%) [31]. Peripheral neuropathy is often present in diabetics and is associated with an increased risk of foot ulcerations and amputations [32]. The Eurodiale cohort of 1088 pts with diabetic foot ulcers found a higher pro-
4. Renal dysfunction and PAD

Pts with CKD are at an increased risk of developing PAD, and PAD prevalence is higher among pts with impaired renal function, indicating that these conditions share common risk factors [12]. The Chronic Renal Insufficiency Cohort Study found that inflammatory biomarkers, prothrombotic state, oxidative stress, and insulin resistance are associated with PAD in pts with CKD [41]. CKD is often accompanied by diabetes and anemia, and both contribute to the excess mortality (Figure 1) [42]. In symptomatic PAD pts, reduced glomerular filtration rate was identified as an independent predictor of major adverse cardiovascular events (MACE) and mortality [43,44]. In conclusion, PAD and CKD are quite common and when present together are associated with a very high risk of unfavorable cardiovascular outcomes [12,45].

5. Inflammation and PAD

CRP is a biomarker routinely used in everyday clinical practice and is identified as one of the strongest predictors of future cardiovascular events [46]. CRP is associated with the development and the severity of PAD as well as impaired glucose regulation [47]. The Insulin Resistance Atherosclerosis Study showed a significant linear increase in incident diabetes with increasing quartiles of CRP [48]. The likelihood of PAD in diabetic pts is enhanced by elevated CRP levels (>3 mg/L) with an odds ratio of 8.6 [49]. Furthermore, diabetic pts with higher levels of CRP (>3 mg/L) are at increased risk of developing nephropathy (Figure 1) [50]. CRP promotes a prothrombotic state by several mechanisms including the production of tissue factor, stimulating endothelial cell dysfunction, and increasing activity of plasminogen activator inhibitor-1 (PAI-1) [51]. The prognostic implication of CRP on cardiovascular mortality in diabetic pts was investigated in a cohort of 1059 pts, which showed that diabetic pts with CRP >3 mg/L were almost two times more likely to die from CAD compared to diabetic pts with CRP ≤3 mg/L, independent of other cardiovascular risk factors [52]. On the other hand, conflicting data was reported on the prognostic significance of CRP on all-cause mortality in diabetic pts. Cox et al. found that diabetic pts with CRP levels between 3-10 mg/L had a 2-fold increased risk of death and those with CRP >10 mg/L were more than five times more likely to die compared to pts with CRP ≤1 mg/L [53].

On the contrary, Lowe et al. showed that CRP was associated with an increased risk of mortality when adjusted for age and sex, but after further adjustment it lost its prognostic significance [54]. The prognostic value of CRP on all-cause mortal-
Anemia has been well assessed in ACS and acute aortic syndromes [55,56]. In symptomatic PAD pts stratified according to age and diabetes, CRP was found to be an independent predictor of all-cause mortality within 5 years of follow-up [57]. Increased CRP values were independently associated with all-cause mortality and CV mortality within 2 years, but at longer follow-up periods, the biomarker lost its prognostic significance [58]. According to these results, it seems that CRP is a better predictor of short-term rather than long-term mortality in PAD pts. A recent study showed that symptomatic PAD pts with impaired renal function and elevated CRP values (>5 mg/L) on admission were more than three times more likely to experience MACE than patients with normal CRP and preserved renal function [43].

6. Anemia and PAD

Anemia is quite prevalent among PAD pts and its prevalence is increased in the presence of diabetes and/or renal impairment [59]. Anemia is common in diabetic pts, particularly in those with albuminuria or impaired renal function [60]. In CKD pts anemia is an important risk factor for adverse outcomes, including mortality (Figure 1). Moreover, it is associated with the development and progression of left ventricular hypertrophy, a well-known risk factor for mortality [61]. Prospective studies identified anemia as an independent risk factor for short-and long-term mortality in pts with acute coronary syndrome (ACS) [62]. Among pts undergoing elective open vascular surgery for PAD, anemia was associated with an increased risk of 30-day and 5-year cardiac events, independent of underlying heart failure or renal disease [63]. In a cohort of 1663 pts with symptomatic PAD, anemic pts were more than two times more likely to die compared to pts with normal hemoglobin levels [64]. In line with previous studies, Desormais et al. reported that anemia and its severity are independent predictors of mortality and limb loss in patients hospitalized for PAD [14].

7. Conclusion

Patients with PAD are at an increased risk for MACE, CV mortality, and all-cause mortality. A close correlation between diabetes, renal dysfunction, inflammation, and anemia is present in PAD pts (Figure 1). Diabetes is a risk factor for PAD and CKD. In PAD pts, diabetes is associated with greater disease severity, an impaired quality of life, and increased mortality. CRP and insulin resistance are associated with PAD among CKD pts, and impaired renal function was found to predict mortality in PAD pts. Anemia has an adverse effect on PAD, diabetes, and renal function, increasing the risk of unfavorable outcomes, including death.

Therefore, PAD pts require a multidisciplinary approach with aggressive risk factor management, lifestyle modification, and treatment of associated comorbidities in order to prevent ischemic events and fatal outcomes.

Author contributions

MV gave an idea for the article, participated in drafting the article and gave the final approval. KV reviewed the previously published literature, participated in drafting the article and gave the final approval.

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