MORTALITY IN PATIENTS WITH PAD WITH RESPECT TO GLYCAEMIC STATUS: A REVIEW

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ABSTRACT

Peripheral arterial disease (PAD) is a manifestation of atherosclerosis. Atherosclerosis is a chronic inflammatory process and nonenzymatic glycation is a process of major interest in relation to how risk factors promote atherogenesis. A strong association between diabetes mellitus (DM) and PAD has been established, and the association is related to the duration of DM. Previous studies have revealed a higher prevalence of DM in patients with PAD compared to general populations and populations at risk of developing DM. The typical dyslipidaemia found in patients with PAD is similar to that found in patients with insulin resistance, and an association of HbA1c with atherogenic dyslipidaemia is described. HbA1c has been described as a predictor for DM and of micro and macrovascular disease. 5-year all-cause mortality in PAD is 19–37% and 10-year all-cause mortality is 42-54%. The mortality in PAD increases with age, with the severity of the peripheral vascular disease, and with the coexistence of PAD with coronary artery disease and DM. Patients with DM, defined by glucose criteria, and PAD have an increased mortality compared with patients with PAD alone. Recent studies have shown an association of HbA1c levels with vascular complications and death in patients with DM. No studies could be found that aimed to validate HbA1c against glucose criteria as a predictor for mortality in patients with PAD. Further studies on patients with PAD and DM are needed to identify which is the best diagnostic method to predict mortality in PAD with respect to glycaemic status: the glucose parameters or the HbA1c.

Keywords: Peripheral arterial disease, mortality, diabetes mellitus, glycaemic status, HbA1c.

INTRODUCTION

Peripheral arterial disease (PAD) and diabetes mellitus (DM) represent a major public health challenge. The prevalence of PAD in general populations is reported to be 2.5-20%[1-10] and it is increasing with age.[2,11,12] In populations at moderate-to-high risk of developing PAD, the prevalence of PAD is 23-41%.[13-16] Individuals with DM have twice as high prevalence of PAD as normoglycaemic individuals.[12,17-19] DM is rapidly increasing in prevalence affecting 285 million people worldwide (2010).[20] Patients with PAD are multimorbid and of high age.[21] PAD varies in severity and clinical expression, and about one-third of patients with PAD are asymptomatic.[11,17] DM and smoking are two main risk factors for PAD[22] and patients with PAD are also likely to have coronary artery disease (CAD) and cerebrovascular disease. Cardiovascular diseases are the leading cause of death globally and accounted for 12.9 million deaths (one-fourth of all deaths) in 2010. 1.3 million deaths were due to DM.[23] CAD and cerebrovascular disease are the main causes of death in patients with PAD.[24] The increased cardiovascular risk in patients with PAD appears to be independent of classic risk factors.[25,26]

Despite the high prevalence and mortality in patients with PAD and the strong association between PAD and DM, PAD is underrepresented in diabetes research compared with CAD. The aim of this article is to review the risk of mortality in patients with PAD with respect to glycaemic status.

METHODS

A PubMed search on titles with the words "atherosclerosis pathophysiology", "endothelial dysfunction in diabetes", "peripheral arterial disease and diabetes mellitus", "distribution of peripheral arterial disease", and "peripheral arterial disease", "vascular disease", and a combination of the two latter with "prevalence" AND "mortality" was performed. Additional related citations were identified from reference lists of articles already included for review.

DEFINITIONS

Definition of Peripheral Arterial Disease

PAD is a manifestation of atherosclerosis, a chronic inflammatory process in the arteries causing both stenotic disease and weakness of the arterial wall, presented as aneurysms. Atherosclerosis occurs focally in the arteries with predilection sites proximally in the arteries and at bifurcations.[27] The clinical diagnosis of PAD is based on a resting Ankle-Brachial Index (ABI) <0.9. A reduction in post-exercise ABI is required as a confirmative test in the presence of symptoms and with a normal resting ABI or in individuals at risk of PAD but with a borderline or normal ABI.[26,28] Current guidelines recommend annual inspection of the foot and palpation of peripheral pulses in the femoral, popliteal and pedal vessels. PAD screening with an ABI, and if normal repeated test every 5 years is recommended in patients with DM >50 years of age.[29]

Definition of Diabetes Mellitus and Intermediate Hyperglycaemia

DM is a group of metabolic diseases resulting from defects in insulin secretion, insulin action or both. Traditionally, the diagnosis of DM has been based on glucose criteria defined by fasting plasma glucose (FPG) ≥7.0 mmol/l or a 2-hour post glucose load value of ≥11.1 mmol/l.[30] The International Expert Committee of Diabetes (2009), the American Diabetes Association (2010), and the World Health Organization (WHO) (2011) implemented an HbA1c value of ≥48 mmol/mol (6.5%) as a new additional diagnostic criterion for the diagnosis of DM.[29,31,32] Limitations in the use of HbA1c as a diagnostic criterion for DM include conditions with abnormal red cell turnover and rapidly evolving diabetes. HbA1c is not approved for the diagnosis of gestational diabetes.[29] Furthermore, HbA1c provides no information about the fasting glycaemic state or the postprandial glycaemic state.

According to WHO (1999) criteria, intermediate hyperglycaemia is defined as impaired glucose tolerance, (FPG <7.0 mmol/L and a 2-hour-value between 7.8 mmol/L and 11.1 mmol/L) and impaired fasting glucose (fasting glucose value between 6.1 mmol/L and 7.0 mmol/L with a normal 2-hour-value).[30] Two intermediate HbA1c ranges have been suggested to be used to identify individuals at high-risk for developing DM: 39-46 mmol/mol (5.7-6.4%) (American Diabetes Association) and 42-46 mmol/mol (6.0–6.4%) (the International Expert Committee).[29,33] The WHO has not yet made a statement on HbA1c levels and intermediate hyperglycaemia.

PATHOPHYSIOLOGY

Atherosclerosis

Atherosclerosis is a chronic inflammatory process initiated and facilitated by risk factors such as DM, smoking, hypertension, hyperlipidaemia, obesity, prior inflammatory states, and elevated plasma homocysteine concentrations.[34] The initiation of atherosclerosis takes place due to alterations in the interaction between the endothelium of the artery wall, the haemodynamics of the arterial flow and the blood composition. Strain applied on the endothelial cells by these alterations causes an activation of the endothelium. A factor of major importance for the maintenance of these alterations and the development of atherosclerosis is endothelial dysfunction. Endothelial dysfunction occurs as an imbalance between the normal endothelial function and the hyperfunction of the activated endothelium.[27,35] Endothelial dysfunction is characterised by functional changes in the endothelial cells

affecting vasoconstriction, vasodilatation, growth of vascular smooth muscle, inflammation, and haemostasis, by altering the normal production of nitric oxide (NO), growth factors, adhesion molecules, cytokines, chemokines, and prostacyclins. Lipoprotein particles adhere to the endothelium as a result of the action of adherence molecules, and accumulate in the intima layer of the arterial wall. Chemical modifications of the lipoproteins lead to the recruitment of mononuclear leukocytes and the formation of foam cells. Smooth muscle cell proliferation, accumulation of extracellular matrix, and cell death contributes to the expansion of the atherosclerotic lesion. Finally, neovascularisation and calcification of the atherosclerotic lesion occur.[27,34,35]

Diabetes and Endothelial Dysfunction

Oxidation and nonenzymatic glycation are two processes of major interest in relation to how risk factors promote atherogenesis. In situations with sustained hyperglycaemia, nonenzymatic glycation of lipoproteins is likely to occur. The glycation of low density lipoproteins (LDL) may act as a strain on the endothelium and thereby start a cascade of alterations which may lead to endothelial dysfunction.[35] DM promotes atherosclerosis not only by increased glycation of LDL, but also by affecting the endothelium in the direction of endothelial dysfunction, by dyslipidaemia, and decreased NO bioavailability because of insulin deficiency or defective insulin signalling in endothelial cells.[36] Apoptosis of vascular smooth muscle cells in advanced lesions results in plaque instability and precipitation of clinical events.[37]

ASSOCIATION BETWEEN GLYCAEMIC STATUS AND PAD

A strong association between DM and PAD has been established, which is related to the duration of DM.[38] Previous studies have revealed a higher prevalence of DM in patients with PAD[2,21,39,40] compared to general populations[41-43] and populations at risk of developing DM.[44] A prevalence of pathologic glucose metabolism of 55% and a frequency of diabetes of 29% was found in Norwegian vascular surgery patients defined by the glucose tolerance test.[21] Likewise, Johansen et al.[40] found a prevalence of pathologic glucose metabolism in 57% of patients with PAD. Leibson et al.[38] revealed a co-existence of DM and PAD at 32.5% in out-clinic patients.[38] The Cardiovascular Health Study revealed a relative risk (RR) at 4.05 for DM in patients with PAD defined as ABI <0.9.45. Ogren et al.[17] reported a 29% prevalence of PAD in men with DM compared with 12% in men without DM. The diagnosis of DM was based on a history of DM or FPG ≥6.1 mmol/L. The overall prevalence of PAD in the National Health and Nutrition Examination Survey (1999-2002) was 5.1%, and the prevalence of PAD in participants with DM was 7.5% for HbA1c values <7% and 8.8% for HbA1c values ≥7%. Hyperglycaemia is associated with increased risk of PAD independent of other risk factors.[46]

The typical dyslipidaemia found in patients with PAD is similar to that found in patients with insulin resistance, thus emphasising the association between the two conditions.[23] In 118 participants aged 65–95 years, Martins et al.[47] found an association of HbA1c with atherogenic dyslipidaemia. The distribution and severity of PAD in patients with DM differs from non-diabetic populations. PAD in patients with DM is multisegmental, progresses at a more rapid rate to occlusion, is more likely to proceed to amputation, and has a higher mortality at a younger age compared with non-diabetic patients. The vascular disease presents at a greater severity in the profunda femoris artery and in the arterial segments below the knee in patients with DM. No significant differences in the severity of the vascular disease in the aorta, the iliac arteries, or the superficial femoral arterial segments are seen in patients with DM compared with patients without DM.[48-50] Studies have shown inconsistent results regarding abdominal aortic aneurysms and DM. A tendency toward a negative hazard ratio regarding abdominal aneurismal disease in DM is described, but further studies are needed to investigate this association.[51]

Differences in the Prevalence of DM and Intermediate Hyperglycaemia Among Patients with PAD by HbA1c Values Compared with Oral Glucose Tolerance Test Results

Most studies that investigated the use of HbA1c values against the oral glucose tolerance test (OGTT) as a diagnostic tool for DM, have found reduced prevalence by HbA1c criteria compared with the OGTT criteria. The studies also showed discordance between OGTT and HbA1c values

suggesting that the two methods define different patient categories.[41-44,52,53] In concordance with these results, a recent study on Norwegian vascular surgery patients found that the OGTT and the HbA1c categorised different individuals with DM and intermediate hyperglycaemia. The total prevalence of pathologic glucose metabolism was substantially higher based on HbA1c values than based on the OGTT.[54]

HbA1c and Cardiovascular Disease

HbA1c has been described as a predictor for DM and of micro and macrovascular disease.[55,56] Studies have shown inconsistent results regarding HbA1c and the prediction of cardiovascular disease. A meta-analysis on glycosylated haemoglobin and cardiovascular disease in patients with DM described a corresponding 26% increased risk of PAD for every 1% increase in HbA1c levels.[57] Pradhan et al.[58] found a multivariable adjusted RR of 1.0–1.6 of HbA1c with the incident of cardiovascular events, and concluded that the association largely could be explained by co-existent traditional risk factors. A recent study from van der Heijden et al.[59] (The HOORN study) found that individuals with DM type 2, but not individuals with intermediate hyperglycaemia are at increased risk for a recurrent cardiovascular event compared with individuals with normal glucose metabolism. Cederberg et al.[60] concluded that HbA1c level range of 5.7-6.4% predicted a 10-year risk of developing DM type 2, but cardiovascular disease only in women at HbA1c ≥6.5%. In patients with CAD but without DM, no correlation was found between HbA1c levels and the presence of CAD.[52] In individuals with DM type 2, overweight and high cardiovascular risk, a high baseline HbA1c level was associated with a high cardiovascular and all-cause mortality risk. Crude incidence rates for all-cause mortality increased with the elevation of baseline HbA1c levels.[61]

MORTALITY IN PAD

Patients with PAD have the highest rate of cardiovascular death and major cardiovascular events among patients with cardiovascular disease.[62,63] The excess mortality in patients with PAD compared with patients without PAD is mainly due to cardiovascular death.[22,25,64]

Overall Mortality

5-year all-cause mortality in PAD is 19-37%[4,65,66] and 10-year all-cause mortality is 42-54%.[65,67,68] The mortality in PAD increases with age, with the severity of the peripheral vascular disease and with the coexistence of PAD with CAD and DM.[25,69,70] Mortality is reported to be higher in males than females.[25]

Mortality in PAD Related to Glycaemic Status

Diabetes-associated vascular complications are responsible for 75% of the deaths associated with diabetes.[71-73] DM increases the risk of death from coronary heart disease independent of coexisting risk factors, and the risk increases with the duration of DM. Patients with DM but without prior myocardial infarction have the same risk of subsequent myocardial infarction as patients with a prior infarction but without DM.[72,74,75] A longitudinal study on PIMA Indians found that medial arterial calcification in patients with DM was related to impaired vibration perception, long duration of DM and high plasma glucose concentrations. Patients with DM and medial arterial calcification had 1.5-fold the mortality rate and 5.5-fold the amputation rate compared with patients with DM but without medial arterial calcification.[76] Ogren et al.[17] stated that both DM alone and PAD alone were associated with an increased rate of mortality. No statistically significant increase in mortality was seen among patients with DM and PAD compared with DM alone.[17] In hypertensive adults without cardiovascular disease at baseline, 6-years mortality was 31% in patients with DM and a low ABI, whereas 12% in patients with DM and a normal ABI. In patients with DM, the RR of mortality for those with a low ABI was 2.74. The RR of mortality in patients without DM and with a low ABI was 2.26.[45] The results from Pasqualini et al.[77] reported a 4-year overall mortality to be 34.3% from all causes and 19.5% from cardiovascular causes. The prevalence of DM, based on FPG ≥7.8 mmol/L or current treatment with insulin or oral hypoglycaemic agents, was significantly higher in the critical ischaemia group compared with the intermittent claudication group. Patients with critical limb ischaemia had an excess risk of 3.40 for overall mortality. The prevalence of DM among patients alive at follow-up compared with patients dead at follow-up was the same in the two groups.[77]

Barzilay et al.[78] aimed to determine the long-term survival and predictors of mortality in patients >50 years of age, with and without DM and with coexistence of PAD and CAD (263 DM, 1137 non-DM) for a mean follow-up at 12.8 years. Patients with DM had a significantly higher mortality rate compared with non-diabetics. The presence of DM was an independent risk factor for mortality. In patients with PAD and DM, CAD was especially severe and prognosis was poor.[78] In a retrospective cohort study of patients with an ABI <0.9, Collins et al.[79] reported a 44.5% mortality. Of the total cohort 61.3% had DM. The authors hypothesised from the results that glucose control defined by HbA1c ≤7.0 or FPG ≤140 mmol/mol was protective against death with a hazard ratio of 0.74, p=0.004. As the authors outpoints, these findings should be evaluated in a prospective study.[79]

Leibson and associates[38] studied patients registered at the Mayo Clinic who had PAD, DM or both at baseline. Results showed that individuals with both PAD and DM have twice as high-risk of death as individuals with PAD alone. Progressors of PAD were at increased risk of death compared with non-progressors. The increased risk was only significant for individuals with DM.[38] Recent studies have shown an association of HbA1c levels with vascular complications and death in patients with DM. Results from the ADVANCE study found a 38% risk of macrovascular events and a 38% risk of death for every 1% rise in HbA1c level above 7%. Stratton et al.[80] found a reduction in risk of amputation or death from PAD of 43% per 1% reduction in HbA1c concentration in the UKPDS 35.[80,81] Takahara et al.[82] aimed to investigate prognostic factors in 278 patients undergoing percutaneous transluminal angioplasty for critical limb ischaemia. HbA1c levels were associated with major amputation but no association was found between HbA1c levels and mortality.[82]

CONCLUSION

DM is an established risk factor for micro and macrovascular disease, and a strong association between DM and PAD has been shown. Patients with DM, defined by glucose criteria, and PAD have an increased mortality compared with patients with PAD alone. Recent studies have shown an association of HbA1c levels with vascular complications and death in patients with DM. No studies could be found that aimed to validate HbA1c against glucose criteria as a predictor for mortality in patients with PAD. Further studies on patients with PAD and DM are needed to identify which is the best diagnostic method to predict mortality in PAD with respect to glycaemic status: the glucose parameters or the HbA1c.

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