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A cross-sectional study in type 2 diabetes patients reveals that elevated pulse wave velocity predicts asymptomatic peripheral arterial disease associated with age and diabetes duration

Dora Gašparini [a,b,*,1], Anamaria Zuljani [c,1], Felix M. Wensveen [b], Tamara Turk Wensveen [a,d,e,2]

[a] Center for Diabetes, Endocrinology and Cardiometabolism, Special Hospital for Medical Rehabilitation of Cardiac, Pulmonary and Rheumatic diseases Thalassotherapia Opatija, Maršala Tita 188/1, 51410 Opatija, Croatia
[b] Department of Histology and Embryology, Faculty of Medicine, University of Rijeka, Braće Branchetta 20/1, 51000 Rijeka, Croatia
[c] Department of Emergency Medicine, Clinical Hospital Center Rijeka, Tome Strižića 3, 51000 Rijeka, Croatia
[d] Department of Internal Medicine, Faculty of Medicine, University of Rijeka, Braće Branchetta 20/1, 51000 Rijeka, Croatia
[e] Department of Endocrinology, Diabetes and Metabolic Diseases, Clinical Hospital Center Rijeka, Krešimirova 42, 51000 Rijeka, Croatia

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ABSTRACT

Background: Peripheral arterial disease (PAD) reduces functional capacity and raises cardiovascular risks, but underdiagnosis is common, resulting in less comprehensive care than other cardiovascular conditions. While diabetes has long been viewed as a key risk factor for PAD, recent studies indicate that its impact is influenced by the presence of concurrent cardiovascular risk factors. The aim of this study is to elucidate the intricate relationship between the prevalence of PAD, diabetic complications, and cardiovascular risk factors among asymptomatic patients with type 2 diabetes mellitus (T2DM).

Methods: Ninety-one patients with T2DM and no symptoms or previous diagnosis of PAD were recruited from the outpatient diabetic clinic. Clinical data were extracted from electronic medical records, and the screening for PAD was conducted using MESI mTABLET.

Results: Screening for PAD among asymptomatic individuals with T2DM revealed that 5.49 % of patients exhibit a low ankle-brachial index (ABI). Patients who had previously experienced major adverse cardiovascular events or exhibited albuminuria displayed lower ABI values. Furthermore, a striking 45.05 % of the participants displayed an abnormally high carotid-femoral pulse wave velocity (cfPWV) value, with elevated PWV values correlating with advanced age and longer diabetes duration.

Conclusions: The prevalence of elevated cfPWV is more pronounced than that of decreased ABI in T2DM patients with asymptomatic PAD and is associated with older age and longer diabetes duration, therefore measurement of both ABI and PWV is crucial for the cardiovascular risk assessment protocol for patients with T2DM and timely PAD diagnosis.

1. Introduction

Peripheral Arterial Disease (PAD) affects over 200 million individuals worldwide [1,2] and presents a spectrum of symptoms, from asymptomatic to severe, resulting from localized stenosis or occlusion in large and medium-sized arteries outside coronary and cerebrovascular territories. Moreover, symptomatic PAD is strongly associated with reduced functional capacity and increased risks of cardiovascular morbidity and mortality, underlining its pivotal role as a marker for systemic atherosclerosis [3]. The high burden of PAD is, in part, attributed to underdiagnosis, which results in delayed recognition and management. Research indicates that a substantial portion of cases remain undiagnosed or unnoticed, with many physicians unaware of prior PAD diagnosis despite it being documented in medical records [4].

* Corresponding author at: Center for Diabetes, Endocrinology and Cardiometabolism, Special Hospital for Medical Rehabilitation of Cardiac, Pulmonary and Rheumatic diseases Thalassotherapia Opatija, Maršala Tita 188/1, 51410 Opatija, Croatia.
E-mail address: dora.gasparini@uniri.hr (D. Gašparini).
[1] These authors contributed equally to this work and share first authorship.
[2] This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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This lack of recognition leads to less intensive management for PAD patients compared to those with other cardiovascular disorders such as coronary artery disease (CAD) [5]. Despite ongoing efforts to improve recognition and treatment, the number of individuals affected by PAD and the associated morbidity continue to rise [6], highlighting the critical need for enhanced awareness and care strategies.

Understanding the structural and functional components involved in the pathogenesis of PAD is essential for improving early detection and diagnosis. Reduced arterial lumen diameter due to atherosclerosis, assessed via the ankle-brachial index (ABI) lower than 0.9, raises suspicion of PAD [7]. Functional changes in PAD stem from shifts in arterial wall viscoelasticity, which can be assessed using arterial stiffness measurements [8]. Carotid femoral pulse wave velocity (cfPWV) serves as the non-invasive gold standard for assessing arterial stiffness and is endorsed by international clinical practice guidelines [9,10]. Studies suggest that the risk linked to low ABI and elevated cfPWV values extends beyond limb ischemia, encompassing an elevated risk of cardiovascular morbidity and mortality [11,12].

The multifaceted relationship between PAD and cardiovascular risk becomes even more complex in the context of chronic metabolic dysregulation observed in patients with type 2 diabetes mellitus (T2DM). Diabetes is traditionally considered a major risk factor for the development of PAD, often unrecognized in this cohort due to alterations in nociception, microvasculature and repair mechanisms. However, recent studies suggest that diabetes alone may not be a strong independent risk factor for PAD, but rather its impact depends on the presence of coexisting cardiovascular risk factors [5,13]. How markers of structural and functional changes in PAD correspond with macro- and microvascular diabetic complications and cardiovascular risk (CVR) factors is still incompletely characterized. Therefore, the aim of this study is to determine the correlation between the prevalence of PAD and diabetic complications, as well as established CVR factors, among patients with T2DM.

2. Subjects

Participants were recruited from the outpatient clinic of the Center for Diabetes, Endocrinology, and Cardiometabolism at the Special Hospital for Medical Rehabilitation of Lung, Heart, and Rheumatism, Thalassotherapia Opatija. The study enrolled 91 Caucasian patients diagnosed with T2DM in accordance with American Diabetes Association criteria [14]. These patients were clinically stable with no symptoms or signs of acute disease. Patients with prediabetes, type 1 diabetes mellitus and those previously diagnosed with PAD were not eligible for study inclusion. All participants signed an informed consent form prior to study participation. This study was approved by the Institutional Review Board at Thalassotherapia Opatija (reference number: 01–000-00–236/2). The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice standards.

3. Materials and methods

3.1. Study design

After signed informed consent was obtained, laboratory and clinical data were collected from the electronic medical records. Following a 5-minute rest in a supine position, PAD screening was performed using MESI mTABLET ABI (MESI Ltd., Ljubljana, Slovenia), a wireless diagnostic module with a 3CUFF™ PADsense™ algorithm.

Left and right ABI values were automatically computed by comparing the systolic blood pressure in the right arm with the systolic pressure at the left and right ankles, respectively. ABI values categorize patients into four groups: <0.90 (abnormally low), 0.90–0.99 (borderline), 1.00–1.39 (normal), and above 1.39 (abnormally high). Given the systemic nature of atherosclerosis and the absence of a significant difference between measured right and left ABI ($p > 0.050$), only the lower ABI values were employed for statistical analysis. Additionally, the brachial-ankle pulse wave velocity (baPWV) was automatically determined by measuring the distance between the brachial and ankle cuffs and the time difference between the recorded pulse waves. The cfPWV was estimated by the software based on manually entered patient height.

The New York Heart Association (NYHA) classification system was employed to assess the functional status, categorizing patients as follows: (I) experiencing no limitations in physical activity, (II) encountering slight limitations in physical activity, (III) facing marked limitations in physical activity, or (IV) unable to engage in any physical activity without discomfort [15]. A subset of patients underwent echocardiographic assessments to determine the ejection fraction (EF) of the left ventricle, classifying it as preserved (≥50 %, denoted as HFpEF for heart failure with preserved ejection fraction), mildly reduced (EF 40–49 %, referred to as HFmrEF for heart failure with mildly reduced ejection fraction), or reduced (EF < 40 %, indicated as HFrEF for heart failure with reduced ejection fraction) [15]. Chronic kidney disease staging was conducted based on the estimated glomerular filtration rate (eGFR) and albuminuria level, following the guidelines established by the Kidney Disease Improving Global Outcomes [16].

Furthermore, we computed the hepatic steatosis index (HSI), a predictor for metabolic-associated fatty liver disease. This calculation was performed utilizing the MDApp HSI calculator available online, which takes into account patient sex, body mass index (BMI), aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels, along with the presence of T2DM [17].

3.2. Statistical analysis

Statistical analysis was conducted using GraphPad Prism (GraphPad Software, San Diego, California, United States). For quantitative data, significance was assessed through unpaired t-tests or one-way ANOVA in case of normal distribution, and Mann-Whitney test or Kruskal-Wallis test with Dunn's post-testing in case of abnormal distribution. For qualitative data, the Chi-squared test or Fisher's exact test were applied. Correlation analysis determined Spearman's correlation coefficient. A $p < 0.050$ was considered statistically significant.

4. Results

4.1. Characterization of study participants

The study enrolled ninety-one patients with T2DM who were asymptomatic for PAD. The gender distribution was equal, and the average age was sixty-six years. About 15 percent of the participants were diagnosed with diabetes within the past year, while the mean duration of diabetes in others was nine years. Most study participants have a good regulation of disease, as evidenced by an average glycated haemoglobin A_{1c} (HbA_{1c}) level < 7.5 % (59 mmol/L). Other baseline characteristics of the study cohort are provided in Table 1.

4.2. Abnormally high pulse wave velocity is more common than abnormally low ankle-brachial index in asymptomatic patients with type 2 diabetes mellitus

In our study, PAD screening revealed that 5.49 % of patients exhibited an ABI considered abnormally low. In contrast, 5.49 % displayed a borderline ABI, while a substantial 89.02 % registered a normal ABI (Fig. 1a). Notably, none of the patients exhibited an abnormally high ABI. Subsequent verification of PAD in all patients with positive ABI findings was conducted via Doppler ultrasound. Additionally, in 45.05 % of the study participants an abnormally high cfPWV, defined as values exceeding 10 m/s) [18], has been demonstrated (Fig. 1b). These findings suggest that high PWV is more common than low ABI in asymptomatic patients with T2DM.

Table 1
Characteristics of study participants. Data are mean ± standard deviation (interquartile range) unless otherwise indicated. All patients were on a minimum 3-month stable antidiabetic treatment. SGLT-2i=sodium-glucose transporter-2 inhibitors, GLP-1RA=glucagon-like peptide-1 receptor agonists, DPP-4i=dipeptidyl peptidase-4 inhibitors, KDIGO=Kidney Disease Improving Global Outcomes.

Parameter	Study group (n=91)
Sex, female/male, n (%)	46/45 (50.55/49.45)
Age, years	66 ± 9 (63–72)
Body mass index, kg/m^2	30.7 ± 5.2 (27.1–33.3)
Newly diagnosed, n (%)	14 (15.38)
Diabetes duration, years	9 ± 8 (3–12)
Glycated hemoglobin A_{1c}, %	7.1 ± 1.0 (6.5–7.6)
Glycated hemoglobin A_{1c}, mmol/mol	54 ± 11 (48–60)
Fasting plasma glucose, mmol/L	7.8 ± 1.7 (6.8–8.6)
Fasting plasma glucose, mg/dL	140 ± 31 (122–155)
Antidiabetic treatment, n (%)	
drug-naïve	3 (3.30)
metformin monotherapy	18 (19.78)
SGLT-2i-based	26 (28.57)
incl. basal-oral therapy	*4 (4.40)*
GLP-1RA-based	11 (12.09)
incl. basal-oral therapy	*2 (2.20)*
DPP-4i-based	10 (11.00)
SGLT-2i+GLP-1RA-based	17 (18.68)
incl. basal-oral therapy	*7 (7.69)*
sulfonylurea-based	5 (5.49)
basal-bolus insulin regimen	1 (1.10)
Medical history, n (%)	
dyslipidemia	89 (97.80)
arterial hypertension	84 (92.31)
prior major adverse cardiovascular event	20 (21.98)
incl. elective coronary revascularization	*9 (9.89)*
heart failure	
New York Heart Association classes I/II/III	35 (38.46)/54 (59.34)/2 (2.20)
ejection fraction <40%/40-49%/≥50%	3 (3.30)/5 (5.49)/49 (53.85)
/missing data	*/34 (37.36)*
atrial fibrillation	3 (3.30)
valvular heart disease	1 (1.10)
Diabetic complication rate, n (%)	
diabetic retinopathy	3 (3.30)
diabetic neuropathy	33 (36.26)
diabetic nephropathy (KDIGO classes)	
G1/G2/G3a/G3b	30 (32.97)/50 (54.95)/8 (8.79)/3 (3.30)
A1/A2/A3	71 (78.02)/19 (20.88)/1 (1.10)
Smoking status, n (%)	
current/previous/never	10 (10.99)/23 (25.27)/58 (63.74)

4.3. Older age and long-term diabetes are associated with higher pulse wave velocity in patients with type 2 diabetes mellitus

Next, we aimed to explore potential associations between our findings and various cardiovascular risk factors through subgroup analysis. When comparing participants aged 65 and older to those under 65, we observed a higher PWV in the older group of patients with T2DM (cfPWV 10.20 vs 9.10 m/s, $p = 0.001$; baPWV 15.15 vs 13.60 m/s, $p = 0.001$) (Fig. 1c-e). This trend was further substantiated by a positive correlation between PWV and age (cfPWV r_s 0.34, 95 %CI 0.13–0.51, $p = 0.001$; baPWV r_s 0.39, 95 %CI 0.19–0.55, $p < 0.001$) (Fig. 1f,g). Our analysis also discovered a notably increased cfPWV in male patients compared to their female counterparts (10.20 vs 9.30 m/s, $p = 0.019$) (Fig. 1h-j). However, the higher prevalence ratio of elevated cfPWV among male patients did not reach statistical significance (prevalence ratio, PR 1.597, 95 %CI 1.007 to 2.602; prevalence difference, PD 0.208, 95 %CI −0.011 to 0.403; p = 0.059).

After assessing for the association with non-modifiable cardiovascular risk factors, we tested whether the duration of diabetes (Fig. 1k-m) or glycemic control, as quantified by glycated haemoglobin A_{1c} (Fig. 1n-p) may be associated with PAD screening results. Patients with a diabetes duration exceeding 5 years exhibited a two-fold higher prevalence of elevated cfPWV values compared to those diagnosed within the past 5 years (PR 2.121, 95 %CI 1.218 to 3.987, PD 0.297, 95 %CI 0.069 to 0.479; $p = 0.009$). Additionally, we observed a significantly higher PWV in patients with longer diabetes duration (mean rank differences: cfPWV 0–5 vs 6–10 −18.92, $p = 0.016$; cfPWV 0–5 vs > 10 mean rank difference −20.71, $p = 0.005$; baPWV 0–5 vs 6–10 −17.71, $p = 0.028$; baPWV 0–5 vs > 10—21.09, $p = 0.004$), along with a positive correlation between PWV and the percentage of HbA_{1c} (cfPWV r_s 0.24, 95 %CI 0.03–0.43, $p = 0.021$; baPWV r_s 0.25, 95 %CI 0.04–0.44, $p = 0.018$) (Fig. 1q,r). Conversely, subgroup analysis did not reveal any significant associations between PAD screening results and BMI, nicotine exposure, or levels of low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C) (Fig. S1).

In conclusion, our findings highlight an association between older age with higher pulse wave velocity. Poor diabetes control and prolonged diabetes duration appear to coincide with increased pulse wave velocity in patients with T2DM.

4.4. Patients with albuminuria and prior major adverse cardiovascular events have a lower ankle-brachial index

To determine how the PAD screening results differ in the presence or absence of diabetic complications, we first compared the patient subgroups according to the presence of the two most prevalent microvascular complications. No significant differences in ABI or PWV between the patient subgroups segregated based on the eGFR were detected (Fig. 2.a-c). However, notably lower ABI values were observed in patients with diabetic nephropathy, as determined by a positive result for albuminuria (1.04 vs 1.13, $p = 0.021$) (Fig. 2d). In contrast, PWV exhibited no significant differences between these patient subgroups (Fig. 2e,f). Remarkably, patients with an ACR of 3 mg/mmol or higher displayed a 14-fold higher prevalence of abnormally low ABI compared to those with ACR below 3 mg/mmol (PR 14.200, 95 %CI 2.226 to 91.080, PD 0.186, 95 %CI 0.034 to 0.429; $p = 0.008$). Moreover, we did not detect significant differences in ABI or PWV between patients with a diagnosis of diabetic peripheral neuropathy and those without it (Fig. 2g-i). Additionally, none of the patients with reported diabetic retinopathy exhibited abnormally low or borderline ABI values, but all displayed elevated cfPWV.

Subgroup analysis based on prior major adverse cardiovascular events (MACE) revealed lower ABI in patients with a history of MACE compared to those without (1.06 vs 1.13, $p = 0.011$) (Fig. 2j-l). Furthermore, patients with prior MACE displayed a 14-fold higher prevalence of abnormally low ABI values in comparison to patients with no prior MACE in their medical history (PR 14.200, 95 %CI 2.226 to 91.080, PD 0.186, 95 %CI 0.034 to 0.429; $p = 0.008$). Regarding other complications, neither the functional class of heart failure (Fig. 2m-o) nor the risk for MAFLD, quantified by the Hepatic Steatosis Index (HSI) (Fig. 2p-r), exhibited differences in PAD screening results in our subgroup analysis.

5. Discussion

Our study introduces a potential novel perspective on PWV in the context of PAD detection. Among asymptomatic T2DM patients, it is notable that elevated cfPWV, a non-invasive gold standard for arteriosclerosis assessment, is more prevalent than reduced ABI. The effect of PAD on cardiovascular health has been previously attributed to systemic atherosclerosis [3], a condition that plays a central role in the development of various cardiovascular diseases. Atherosclerosis is a chronic progressive disease characterized by plaque formation and inflammation within arterial walls. Plaques gradually narrow and harden the arteries, resulting in reduced blood flow. Understanding atherosclerosis is fundamental for a comprehensive exploration of arteriosclerosis, a broader category of vascular diseases marked by changes in arterial wall

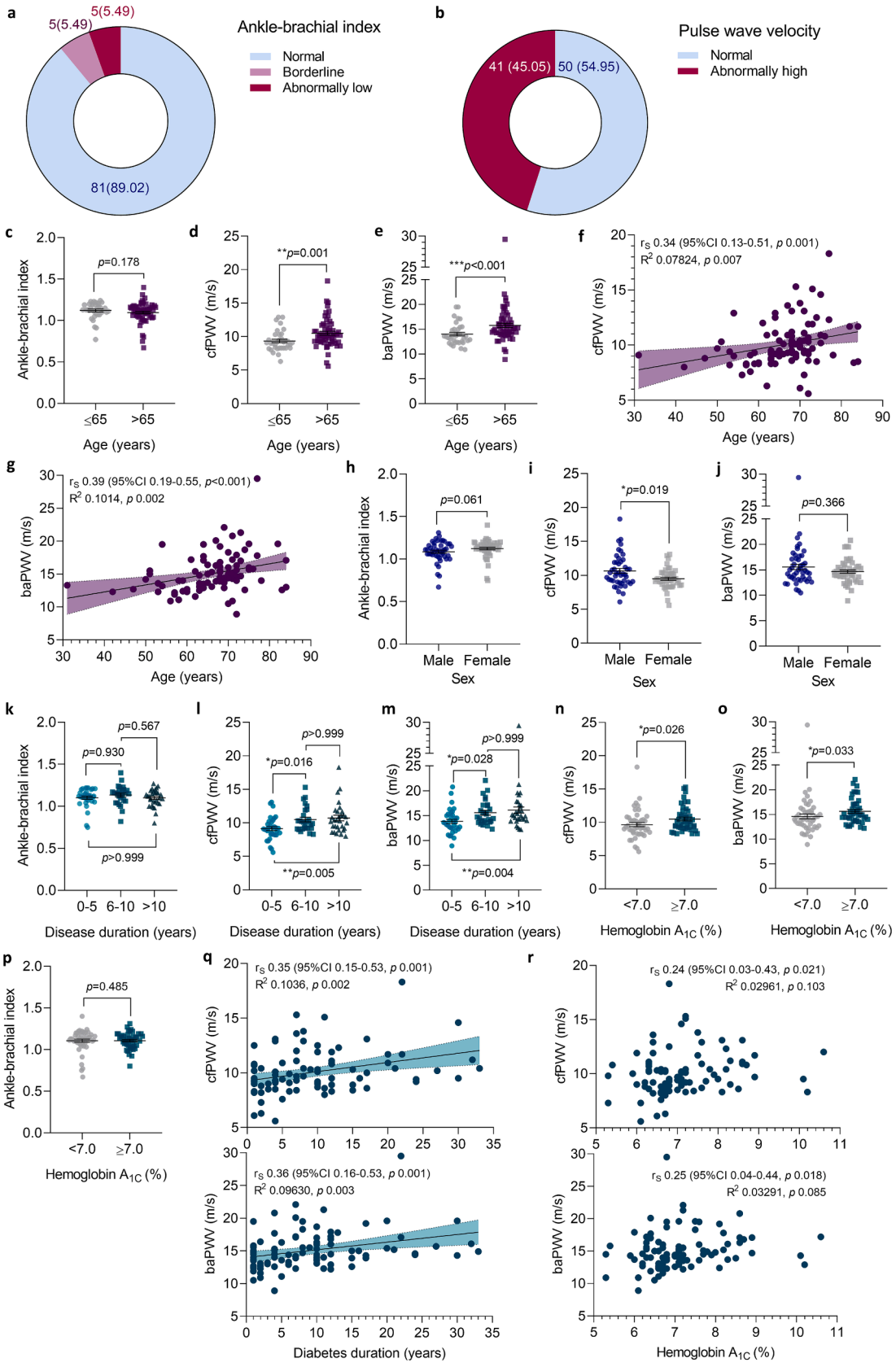

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Fig. 1. Older age and long-term diabetes are associated with higher pulse wave velocity in patients with type 2 diabetes mellitus. Ankle-brachial index (ABI) and pulse wave velocity (PWV) were measured with a peripheral artery disease (PAD) screening tool in asymptomatic patients with type 2 diabetes mellitus. (a,b) PAD screening results are shown as n (%) in participant subgroups. Subgroup definition is as follows: (a) normal (1.00–1.39), borderline (0.90–0.99) and abnormally low (<0.90) ABI, and (b) normal (<10.0 m/s) or abnormally high (≥10.0 m/s) carotid-femoral PWV (cfPWV). Abnormally high (≥1.40) ABI was not detected in any participant. (c-e) ABI and PWV values were compared between participants of up to 65 years of age (n = 35) or above (n = 56). (f,g) Spearman correlation analysis and linear regression model were used to determine the nature of the association between pulse-wave velocity and age in all participants (n = 91). (h-j) ABI and PWV values were compared between male (n = 45) and female (n = 46) participants. (k-m) ABI and PWV values were compared between participants with diabetes duration of up to 5 years (n = 34), between 5 and 10 years (n = 27) and longer than 10 years (n = 30). (n-p) ABI and PWV values were compared between participants with glycated haemoglobin A_{1c} (HbA_{1c}) below 7.0 % (n = 47) and 7.0 % or above (n = 44). (q,r) Spearman correlation analysis and linear regression model were used to determine the nature of the association between pulse-wave velocity and (q) diabetes duration and (r) HbA_{1c} in all participants (n = 91). Data are shown as individual values, mean and standard error of mean. Statistical significance at two-tailed $p^*<0.050$, $^{**}<0.010$ and $^{***}<0.001$ was determined by Mann-Whitney test (c-e,h-j,p) and Kruskal-Wallis with Dunn's multiple comparisons test (k-o). baPWV = brachial-ankle PWV.

thickness and elasticity. Arteriosclerosis harms vascular compliance through an increase in arterial stiffness and the acceleration of the pulse wave reflection, as well as premature reflections due to arteriosclerotic bifurcations and obstructions [19]. Premature reflections cause an increase in the aortic augmentation index (AIx) and a decrease in the subendocardial viability ratio (SEVR) which may cause an acceleration in CAD [19]. However, recent findings also show that impaired peripheral perfusion can influence myocardial perfusion directly through changes in pulse wave reflection [19]. The elevated cfPWV values, therefore, carry substantial prognostic significance, given their associations with both macro- and microvascular CAD, reduced coronary blood flow reserve, and cerebrovascular disease, resulting in a higher incidence of MACE in these cohorts [20–24]. Conflicting findings exist regarding the relationship between PWV and ABI. Research reports have demonstrated various associations, including positive or negative correlation and even a U-shaped association between ABI and PWV [25–28]. These disparities may, in part, be attributed to variations in the characteristics of the studied populations. We hypothesize that PWV values gradually increase in patients with cardiometabolic risk factors and may potentially be a useful surrogate marker with higher sensitivity for peripheral atherosclerosis detection in asymptomatic T2DM patients. In middle-aged Japanese men without PAD, mixed model linear regression analysis of the repeated-measurement data obtained over the 9-year observation period demonstrated that an annual increase of baPWV was associated with ABI [29]. However, it remains uncertain how long it takes for ABI values to change after PWV increases and whether more frequent follow-ups are warranted for T2DM patients with elevated PWV. Notably, Piko et al. also hypothesized that slight reductions in ABI, which remain within the normal range, may impact the propagation of pulse waves [30]. Failing to consider other markers reflecting functional changes in PAD, such as cfPWV, may result in overlooking the initial alterations in peripheral arteries. Our findings underscore the importance of incorporating multiple screening markers for PAD, especially in asymptomatic high-risk patient populations.

Previous research has established an association between prolonged diabetes duration (≥8 years) and a significantly increased risk of CAD [31]. Surprisingly, our study showed a significant association between lower ABI values and a history of MACE, while no correlation was observed with the duration of diabetes. Remarkably, the high prevalence of elevated cfPWV in our study, particularly among elderly patients with prolonged diabetes duration, suggests a progressive increase in this metric among individuals with T2DM. While PAD is relatively infrequent in younger individuals, its prevalence rises with age, affecting over 20 % of individuals aged over 80 [5]. This age-related increase can be attributed to the fragmentation of elastic fibers, alterations in vascular tone, and elevated blood pressure, all of which are recognized as contributing factors to the elevated cfPWV values observed in older patients [32]. Other factors, such as sex and BMI, have been suggested to influence arterial stiffness parameters, as well. While there is evidence from a *meta*-analysis suggesting that lifestyle modifications, statin and antihypertensive medication use might not reduce the relative excess risk of occlusive vascular disease in women with diabetes [33], results from studies investigating the association between BMI and arterial stiffness parameters remain contradictory [30].

Blood pressure is another well-established contributing factor of cfPWV increase. In our study, over 90 % of patients required pharmacotherapeutic management for arterial hypertension. However, studies indicate that only 30–50 % of patients with PAD achieve target blood pressure levels [34,35]. A large-scale study involving more than 13,000 participants, assessing the presence of vascular-related diseases such as hypertension, diabetes, CAD, stroke and PAD, revealed that associations between arteriosclerosis and vascular-related disease, other than hypertension, were largely explained by the association with hypertension [36]. For patients with symptomatic PAD, iliac and femoropopliteal artery angioplasty significantly reduced aortic and brachial blood pressure values, with more pronounced effects observed in patients with higher baseline BP values and more proximal lesions [37]. This underscores the pivotal role of arterial hypertension in the development of arteriosclerosis and highlights the importance of appropriate antihypertensive treatment in patients with PAD, as well as its timely diagnosis.

The impact of antidiabetic treatment on the development and progression of PAD is still poorly understood. In our study, we observed no difference in ABI or PWV values across various treatment groups (data not presented). In recent years, concerns arose regarding the potential association between canagliflozin and an increase in lower limb fractures and amputations, prompted by findings from the CANVAS Program (CANagliflozin cardioVascular Assessment Study) [38]. However, several studies have revealed no escalation in extended major lower extremity amputations in patients treated with sodium-glucose cotransporter-2 inhibitors and incretin-based therapies compared to other medications in patients suffering both from T2DM and PAD [38,39]. Importantly, pre-existing PAD emerged as the primary risk factor for amputation [39]. On the contrary, recent research unveiled a significantly reduced risk of major adverse limb events in patients using glucagon-like peptide 1 receptor agonists compared to those prescribed dipeptidyl-peptidase 4 inhibitors [40]. Further large-scale interventional studies are warranted to establish recommendations on the additional therapeutic benefits of various antidiabetic agents on structural and functional parameters reflecting different stages of peripheral atherosclerosis.

5.1. Study limitations

While our study has provided valuable insights into the association between PWV, age and T2DM duration, it is imperative to address the study limitations to ensure a comprehensive understanding of our findings. First, our study cohort consisted of patients with T2DM recruited from a single center, specifically the diabetes outpatient clinic. These patients demonstrated high levels of adherence to treatment and follow-up, maintained glycemic values close to the target level, and exhibited a low overall incidence of chronic complications. However, it is essential to acknowledge that this cohort may not fully represent the diversity of the diabetes population. Nevertheless, this allowed us to explore our research question within an asymptomatic patient group. Second, our sample size was limited, consisting exclusively of Caucasian

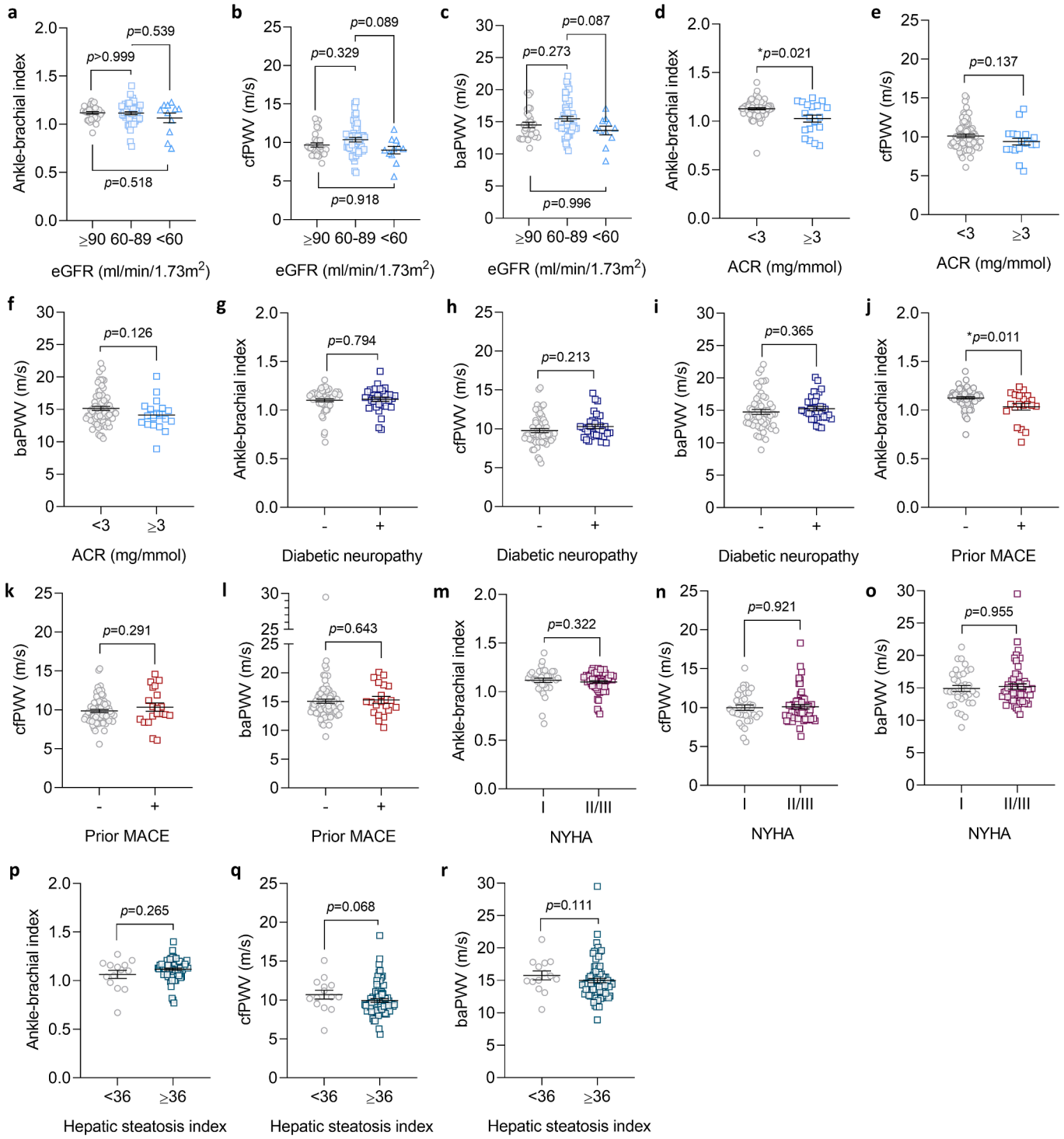

Fig. 2. Prior major adverse cardiovascular events and albuminuria are associated with a lower ankle-brachial index. Ankle-brachial index (ABI) and pulse wave velocity (PWV) were measured with a peripheral artery disease (PAD) screening tool in asymptomatic patients with type 2 diabetes mellitus. (a-f) ABI and PWV values were compared between participants according to the presence of diabetic nephropathy. (a-c) Based on the estimated glomerular filtration rate (eGFR), participants were classified into three grades (n = 30, n = 50 and n = 11, respectively). (d-f) Based on the albumin-creatinine ratio (ACR), participants were classified into two grades (n = 71 vs. n = 20). (g-l) ABI and PWV values were compared between participants according to the presence of (g-i) diabetic neuropathy (n = 58 vs. n = 33), and (j-l) prior major adverse cardiovascular events (MACE, n = 71 vs. n = 20). (m-o) ABI and PWV values were compared between participants based on the New York Heart Association (NYHA) functional class (n = 35 vs. n = 56), and (p-r) hepatic steatosis index (n = 14 vs. n = 77). Data are shown as individual values, mean and standard error of mean. Statistical significance at two-tailed $p^*<0.050$, $^{**}<0.010$ and $^{***}<0.001$ was determined by Mann-Whitney test (d-r) and Kruskal-Wallis with Dunn's multiple comparisons test (a-c). See also Fig. S1. baPWV = brachial-ankle PWV, cfPWV = carotid-femoral PWV.

patients, which raises concerns regarding the generalizability of our findings to other ethnic groups. Consequently, our results would benefit from verification in diverse populations. Moreover, we did not investigate other potentially relevant factors that could influence arterial stiffness, such as daily levels of physical activity.

The measurement tool used in our study was not externally validated beyond Doppler verification of positive screening results, although previous studies indicate a close correlation between values assessed by Doppler and the oscillometric method [25]. Furthermore, all measurements were conducted only once in the present study for practical reasons, which is a potential source of imprecision. Employing multiple measurements would likely enhance the robustness of our findings by reducing measurement variability.

The cross-sectional design of the study prevents the establishment of causal relationships. Thus, we emphasize the need for prospective long-term studies with larger sample sizes to explore the applicability of PWV in assessing cardiovascular prognosis among high-risk patients with T2DM. Additionally, interventional studies that explore how different glucose-lowering treatment regimens impact ABI and PWV values in these patients would provide valuable insights. To advance our understanding of blood flow and vessel wall stiffness in diabetes, the next crucial step involves initiating multi-center studies with a longitudinal design.

6. Conclusions

Our study highlights a noteworthy finding: the prevalence of elevated cfPWV is more pronounced than that of decreased ABI in T2DM patients with asymptomatic PAD and is associated with older age and longer diabetes duration. In contrast, lower ABI values in our patients were associated with albuminuria and previous MACE, further supporting the addition of this valuable measurement into the cardiovascular risk assessment array, especially when end-organ damage has already occurred. Nevertheless, PAD exhibits a relatively high prevalence among asymptomatic individuals with diabetes. In clinical practice, adopting the routine use of an affordable PAD screening tool would significantly enhance the detection of subclinical peripheral atherosclerosis in diabetic patients. Building on this observation, we advocate for the employment of a multi-point measurement approach for both ABI and PWV as a simple tool that can be seamlessly integrated into the diagnostic and cardiovascular risk assessment protocol for patients with T2DM and timely diagnosis of PAD. Our findings prompt further investigation into the significance of cfPWV as a potential predictor of cardiovascular morbidity and mortality in this specific patient demographic.

CRediT authorship contribution statement

Dora Gašparini: Methodology, Investigation, Formal analysis, Writing – original draft, Project administration, Visualization. **Anamaria Zuljani:** Investigation, Formal analysis, Writing – review & editing. **Felix M. Wensveen:** Resources, Writing – review & editing. **Tamara Turk Wensveen:** Conceptualization, Resources, Supervision, Writing – review & editing, Funding acquisition.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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