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Decline in ankle-brachial index is stronger in poorly than in well controlled diabetes: Results from the Heinz Nixdorf Recall cohort study

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HIGHLIGHTS

- Poorly controlled diabetes is associated with decline of ankle-brachial index (ABI).
- Diabetes newly diagnosed by HbA1c is not associated with ABI decline after 10 years.
- Incident Mönckeberg Disease is very rare in subjects with diabetes at baseline.

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ABSTRACT

Background and aims: The ankle-brachial index (ABI) is a marker of atherosclerosis and a diagnostic criterion for peripheral arterial disease (PAD). We studied the association between HbA1c and ABI in subjects with and without diabetes.

Methods: In the Heinz Nixdorf Recall Study, a population-based cohort study in Germany (N = 4,814, age 45–75 years), ABI was measured at baseline, at 5- and 10-year follow-up. Subjects with ABI < 0.9, ABI > 1.4 or self-reported PAD at baseline were excluded from analyses. In 3199 participants, we assessed associations between HbA1c and incident PAD (ABI < 0.9) and change in ABI, respectively, using logistic and linear regression models. Subjects without diabetes, with HbA1c < 5.7% were used as reference group.

Results: Compared to the reference group, 10-year decline in ABI was −0.066 (95% confidence interval: −0.117; −0.016) and −0.021 (−0.063; 0.021) in subjects with poorly (≥7.0% HbA1c) and well (< 7.0% HbA1c) controlled previously known diabetes; −0.010 (−0.054; 0.034) in those with newly detected diabetes diagnosed by HbA1c ≥ 6.5%, and −0.005 (−0.023; 0.013) in those without diabetes, with HbA1c 5.7–6.4%. For poorly controlled diabetes, odds ratios for low ABI (< 0.9) were 3.5 (1.6–7.9), and 3.1 (1.3–7.0) after 5- and 10-year follow-up, respectively. The incidence of Mönckeberg disease (ABI > 1.4) was low (6/288 (2.4%) over 5 years).

Conclusions: Decline in ABI was stronger in poorly than well-controlled diabetes. Subjects with newly detected diabetes diagnosed by the new HbA1c criterion (≥6.5%) did not show an increased decline in ABI over 10 years.

1. Introduction

An increase in HbA1c is associated with an increased risk of cardiovascular disease (CVD) in subjects with diabetes, but also in those without diabetes [1–3]. In a meta-analysis of ten studies on persons with type 2 diabetes, an increase of HbA1c by 1% was related to a relative increase of CVD risk by 18% (relative risk (RR) = 1.18, 95% confidence interval (CI): 1.10–1.26) [1]. In the Atherosclerosis Risk in Communities (ARIC) study, an HbA1c increase was related to an increased CVD risk even in the prediabetic range [3]. A related question refers to the association of HbA1c with subclinical atherosclerosis. Recently, it was shown that in subjects with diabetes, progression of

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coronary artery calcification was stronger in poor glycemic controls (indicated by HbA1c ≥ 7.0%) than in good glycemic controls [4–6]. In a non-diabetic population, a cross-sectional positive association between HbA1c and carotid intima-media thickness was observed [7].

The ankle-brachial index (ABI) is a general marker of atherosclerosis, and, moreover, a diagnostic criterion for peripheral artery disease (PAD) [8]. A low ABI indicates a high risk of myocardial infarction, stroke or death [9,10], and the risk of total mortality may even increase in persons with ABI ≤ 1.1 [11]. Several studies on ABI and CVD events, and ABI and CVD mortality, respectively, showed U-shaped associations [12–14]; in other studies, however, an increased CVD risk was only found in low, but not high ABI [13,15]. So far, there are few prospective studies on the HbA1c ABI association, which indicates that higher levels of HbA1c are a risk factor for a decrease of ABI or an increase of PAD incidence [16–19].

Patients with diabetes have a particular poor prognosis if they also suffer from PAD [20]. Therefore, a first aim of our study was to assess whether glycemic control has an impact on ABI change in patients with diabetes. If so, good glycemic control might contribute to preventing PAD in subjects with diabetes. A second aim of our study was to use the new HbA1c based diagnostic criterion for diabetes [21], and to assess whether persons with HbA1c defined prediabetes and newly detected diabetes, respectively, have a higher risk of ABI decline. Third, ABI can also increase over time in some persons and can result in Mönckeberg disease (MD) [22,23]. Therefore, our third aim was to look at associations between HbA1c and incident MD. Our analyses were done with data from the German population-based Heinz Nixdorf Recall cohort study with measurement of ABI at three points in time.

2. Materials and methods

2.1. Study population

The Heinz Nixdorf Recall study is a population-based prospective cohort study conducted in three large adjacent cities (Bochum, Essen, Mülheim) in the Ruhr-region in North-Rhine-Westphalia in Germany. The study rationale and design have been described in detail elsewhere [24]. In short, the cohort comprises a total of 4814 subjects (49.8% men, aged 45–75 years). The baseline visits were performed between 2000 and 2003. The first follow-up visits took place between 2005 and 2008, and the second follow-up visits took place between 2011 and 2015. The median follow-up was 5.1 years for the first follow-up period, and 5.2 years for the second follow-up period. Data assessment at baseline and at follow-up visits included a self-administered questionnaire, face-to-face interviews, and a physical examination including, among others,anthropometric measurements and comprehensive laboratory tests. 3199 subjects formed the analysis set for longitudinal analyses (cf. flow-chart in Fig. 1). In particular, we excluded persons with ABI < 0.9 or ABI > 1.4 at baseline, persons with self-reported PAD, and those with a history of coronary artery disease.

The study was approved by the Ethical Committee of the Medical Faculty of the University Clinic Essen. All participants gave their written informed consent.

2.2. Measurement of exposure, outcome and covariates

HbA1c was measured using immunonephelometry at 340/700 nm (BNII nephelometer, Dade-Behring, Deerfield, Illinois, USA). Previously known diabetes was stated if subjects gave a self-report of physician's diagnosis or took antidiabetic drugs (ATC code A10). In those with previously known diabetes, duration of diabetes was calculated from self-reported age at diagnosis.

The standard protocol for measurement of ABI was used at all three visits to the study center [23]. ABI was calculated per leg as the ratio of the highest ankle artery systolic pressure measured either in the posterior tibial or the dorsalis pedis artery and the highest brachial pressure measured either in the right or the left arm. The smaller of two ABI values was used for this study. Medical history of PAD was determined from a standardized interview, which included questions on known PAD and on present or prior treatment of PAD [23].

Data on weight were collected with measuring systems of the company 'seca' (seca gmbh & co. kg, Hamburg, Germany). Body mass index (BMI) was calculated as a participant's weight in kilogram divided by the height squared in meters. Blood pressure was determined from the mean value of the 2nd and 3rd of three measurements taken at least three minutes apart (Omron 705_CP, OMRON, Germany) and classified according to JNC-VII threshold values. Hypertension was defined as stage 1 or 2 hypertension or taking antihypertensive medication. Triglyceride and cholesterol serum concentrations were measured with an automatic analyzer (ADVIA 1650, Siemens Medical Solutions, Erlangen, Germany). Information on kind and duration of exercise performed in the preceding month was used to estimate metabolic equivalents per week [25]. Smoking status, use of statins (ATC code C10AA), and use of antihypertensives (ATC code C02) were gathered from interviews at baseline examination. Smoking was grouped into three categories (current, former, never smoker). Participants were asked to bring all packages of drugs they had taken during the last 7 days, and drugs were recorded by scanning the bar codes of the packages. Anatomical Therapeutical Chemical (ATC) codes were obtained using the IDOM software.

2.3. Statistical analyses

For all regression models, the following five categories of HbA1c were used for the exposure variable: previously known diabetes with HbA1c ≥ 7.0%; previously known diabetes with HbA1c < 7.0%; no previously known diabetes with HbA1c ≥ 6.5%; no previously known diabetes with HbA1c 5.7–6.4%; no previously known diabetes with HbA1c < 5.7% (reference category).

Separately for the 5-year and for the 10-year follow-up period, we fitted two sets of linear regression models to estimate regression coefficients for the association between HbA1c categories and change of ABI. The data set for the 5-year follow-up included 3158 persons with ABI data at baseline and at first follow-up, the data set for the 10-year follow-up included 2331 persons with ABI data at baseline and at second follow-up. Moreover, we fitted two sets of multinomial logistic regression models to estimate odds ratios for the associations between HbA1c categories and a trichotomous outcome (incident PAD (ABI < 0.9) and incident Mönckeberg disease (ABI > 1.4) *versus* 0.9 ≤ ABI ≤ 1.4 (reference)) for the 5-year and the 10-year follow-up period. In addition, a linear mixed effect model was fitted to assess changes of ABI between the visits to the study center. This analysis included all 3199 persons with ABI data either at the first or the second follow-up visit to the study center. We used the SAS procedure PROC MIXED, and among RANDOM and REPEATED statements, we chose repeated measures with unstructured covariance, which had the lowest value of Akaike Information Criterion.

In all regression analyses, two models were fitted: an age-sex adjusted model; and a model additionally adjusted for BMI, smoking, physical activity, systolic blood pressure, diastolic blood pressure, triglycerides, HDL cholesterol, LDL cholesterol, intake of statins, intake of antihypertensive medication. Adjustment for diabetes duration does not make sense for the whole study group because this variable cannot be applied to persons without diabetes, and because diabetes duration is the defining element to distinguish newly detected from previously known diabetes. Therefore, we additionally adjusted for diabetes duration in a sensitivity analysis, which only included participants with previously known diabetes.

All statistical analyses were performed using SAS version 9.4. We calculated and reported confidence intervals to assess the precision of our estimates because our goal was estimation and not significance testing [26,27]. We wish to avoid publication bias by preferential

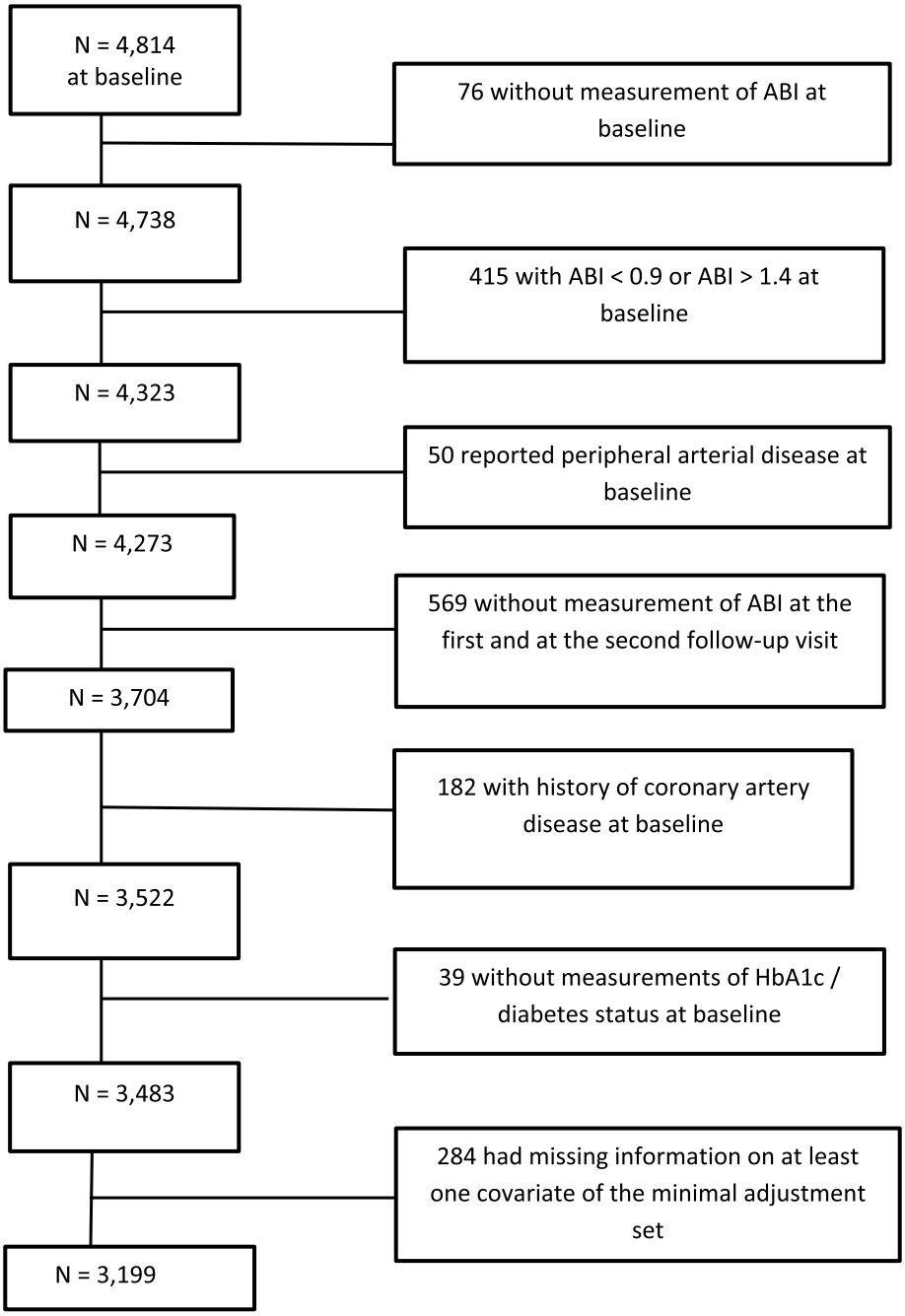

Fig. 1. Flow-chart of subjects entering the data analysis set.

reporting of significant results. Instead, we judge the value of our estimates by their precision and validity.

3. Results

Among 193 persons with previously known diabetes, 76 (39.4%) had HbA1c ≥ 7.0% indicating poor glycemic control. Compared to persons with well-controlled diabetes, those with poorly controlled diabetes had higher BMI, higher systolic blood pressure, more often used anti-hypertensives, less favorable cholesterol concentrations, and higher concentrations of triglycerides (Table 1). Among 3006 persons without previously known diabetes, 96 (3.2%) had newly detected diabetes diagnosed by the new HbA1c criterion (≥6.5%). Subjects with newly detected diabetes had higher BMI, higher systolic and diastolic blood pressure, higher concentrations of triglycerides, and they more often used anti-hypertensives and statins than those free of diabetes.

Patients with poorly controlled, previously known diabetes showed the strongest decline in ABI (Fig. 2). Compared to those without diabetes and with HbA1c < 5.7%, subjects with poorly controlled, previously known diabetes showed a large decline in ABI (−0.034 (95% CI: −0.070 to 0.001) over 5 years; −0.066 (95% CI: −0.117 to −0.016) over 10 years, respectively) (Table 2, model 2). The decline in ABI was smaller in those with well-controlled, previously known diabetes, and newly detected diabetes (−0.021 (95% CI: −0.063 to 0.021), and −0.010 (95% CI: −0.054 to 0.034), respectively, over 10 years).

In the mixed linear model, the coefficient of interaction with time was −0.036 (−0.059 to −0.014) for poorly, and −0.008 (−0.026 to 0.011) for well-controlled diabetes. These coefficients of interaction can be interpreted as change of ABI per 5-year period of follow-up.

Table 1
Baseline characteristics stratified by category of glucose regulation: the Heinz Nixdorf Recall study.

	Glucose regulation (HbA1c)				
	No previously known diabetes			Previously known diabetes	
	< 5.7%	5.7–6.4%	≥6.5%	< 7.0%	≥7.0%
N	2304	606	96	117	76
Age (years)	58.1 ± 7.4	60.6 ± 7.5	61.1 ± 6.9	60.2 ± 7.5	61.4 ± 7.7
Sex (males) (%)	45.0	46.5	60.4	53.9	54.0
BMI (kg/m^2)	27.0 ± 4.1	28.6 ± 4.7	30.2 ± 4.6	30.2 ± 5.7	31.1 ± 5.8
Systolic blood pressure (mmHg)	129.9 ± 19.8	132.1 ± 19.6	141.1 ± 23.9	135.7 ± 17.9	140.3 ± 19.7
Diastolic blood pressure (mmHg)	80.9 ± 10.6	81.3 ± 10.8	85.3 ± 13.0	81.2 ± 9.5	81.7 ± 10.4
Use of anti-hypertensives (%)	26.3	34.7	43.8	53.0	64.5
HDL cholesterol (mg/dl)	60.6 ± 17.1	55.9 ± 15.9	52.8 ± 14.5	52.6 ± 15.1	48.9 ± 15.0
LDL cholesterol (mg/dl)	146.4 ± 35.8	151.1 ± 36.3	149.3 ± 34.9	135.8 ± 35.3	140.2 ± 35.4
Triglycerides (mg/dl)	115.0 (84.0; 162.0)	133.0 (99.0; 184.0)	160.0 (111.5; 217.5)	150.0 (100.0; 216.0)	173.0 (117.0; 238.0)
Use of statins (%)	5.4	9.4	16.7	12.8	7.9
Smoking					
Never (%)	44.1	46.4	35.4	42.7	48.7
Former (%)	33.5	31.7	47.9	41.0	25.0
Current (%)	22.4	22.0	16.7	16.2	26.3
Physical activity (metabolic equivalents/week)	31.3 (14.7; 56.8)	33.0 (16.0; 59.1)	39.3 (22.3; 63.3)	22.5 (10.5; 54.8)	24.7 (9.0; 46.1)
Duration of diabetes (years)	–	–	0	4 (2; 9)	7 (3; 12)
ABI at baseline (%)	1.14 ± 0.11	1.14 ± 0.11	1.15 ± 0.11	1.15 ± 0.12	1.12 ± 0.13

ABI: ankle brachial index.
Values are expressed as mean ± standard deviation, median (first quartile, third quartile), or proportion (%).

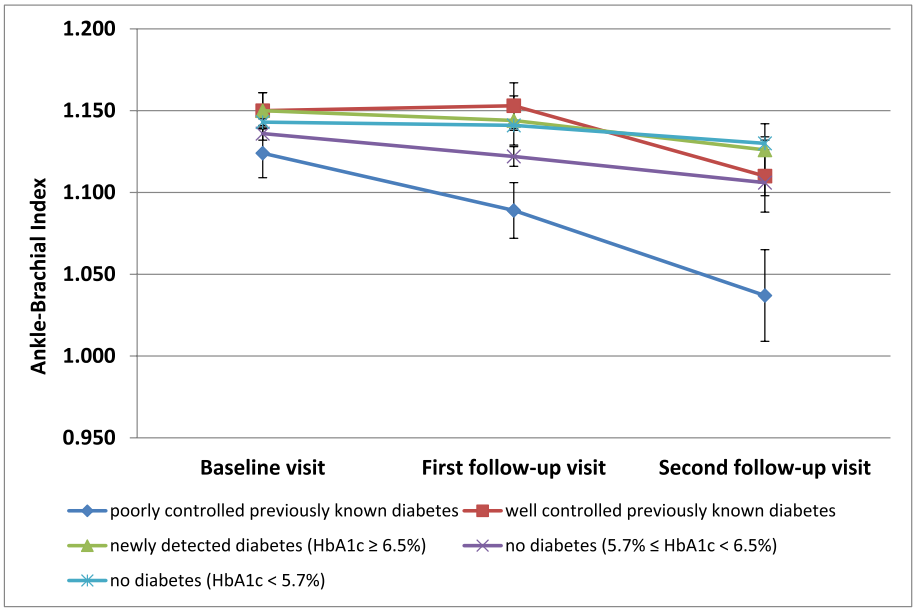

Fig. 2. Ankle-brachial index (± standard error) at baseline, first and second follow-up visit by HbA1c level of subjects with and without previously known diabetes.

Compared to patients free of diabetes and HbA1c < 5.7%, those with poorly controlled, previously known diabetes had a larger odds of incident PAD defined by ABI < 0.9 (OR = 3.5 (95% CI: 1.6 to 7.9) over 5 years, and OR = 3.1 (95% CI: 1.3 to 7.0) over 10 years) (Table 3, model 2). Over 10 years, subjects with well-controlled, previously known diabetes and newly detected diabetes did not have larger odds of ABI shifting below 0.9 than those without diabetes and HbA1c < 5.7% (OR = 0.9 (95% CI: 0.3 to 2.7), and OR = 0.4 (95% CI: 0.1 to 1.7), respectively).

In patients with previously known or newly detected diabetes, the incidence of Mönckeberg disease was very low. In 288 with diabetes at baseline, 6 (2.4%) had incident ABI > 1.4 at 5-year follow-up, and in 166 with diabetes at baseline, three (1.8%) had incident ABI > 1.4 at 10-year follow-up.

In a sensitivity analysis, we compared poorly controlled, previously known diabetes to well-controlled, previously known diabetes with additional adjustment for duration of diabetes. In the linear regression model with change of ABI as dependent variable, decline in ABI was stronger in previously known diabetes compared to well controlled diabetes (−0.045 (95% CI: −0.095 to 0.004) over 5 years; −0.031 (95% CI: −0.100 to 0.037) over 10 years). Diabetes duration was associated with ABI decline (−0.0024 (95% CI: −0.005 to 0.000) per year for the 5-year follow-up; −0.0048 (95% CI: −0.0095 to −0.0001) for the 10-year follow-up).

In sex-specific analyses of the 5-year follow-up, the adjusted odds ratios for the associations between poorly and well controlled diabetes and incident ABI < 0.9 were 3.4 (95% CI: 1.0 to 11.5), and 2.0 (0.6–7.4), respectively, in men, and they were 4.5 (1.4–14.3) and 1.1

Table 2
Regression coefficients (95% confidence intervals) for the associations between HbA1c categories and change of ABI during 5-year and during 10-year follow-up.

Previously known diabetes	HbA1c (%)	ß (95% CI) for 5-year follow-up				ß (95% CI) for 10-year follow-up			
		N	Δ ABI (Std)	Model 1	Model 2	N	Δ ABI (Std)	Model 1	Model 2
Yes	≥ 7.0	76	−0.035 (0.148)	−0.034 (−0.069; 0.001)	−0.034 (−0.070; 0.001)	44	−0.095 (0.178)	−0.077 (−0.127; −0.027)	−0.066 (−0.117; −0.016)
Yes	< 7.0	116	0.002 (0.164)	0.003 (−0.026; 0.032)	−0.001 (−0.030; 0.028)	65	−0.039 (0.158)	−0.024 (−0.066; 0.017)	−0.021 (−0.063; 0.021)
No	≥ 6.5	96	−0.006 (0.150)	−0.006 (−0.038; 0.025)	−0.007 (−0.039; 0.024)	57	−0.033 (0.147)	−0.018 (−0.062; 0.026)	−0.010 (−0.054; 0.034)
No	5.7–6.4	596	−0.014 (0.160)	−0.012 (−0.026; 0.002)	−0.010 (−0.024; 0.004)	421	−0.029 (0.168)	−0.010 (−0.028; 0.008)	−0.005 (−0.023; 0.013)
No	< 5.7 (ref)	2274	−0.001 (0.151)	0	0	1744	−0.015 (0.168)	0	0

Model 1: adjusted for age and sex.
Model 2: adjusted for age, sex, BMI, smoking, physical activity, systolic blood pressure, diastolic blood pressure, triglycerides, HDL cholesterol, LDL cholesterol, intake of statins, intake of antihypertensive medication.

(0.3–5.1), respectively, in women. For the 5-year follow-up, the regression coefficients for the association between HbA1c categories and change of ABI were −0.021 (−0.074 to 0.033), and −0.035 (−0.078 to 0.009), respectively, in men, and −0.050 (−0.098 to −0.002), and +0.037 (−0.002 to 0.076), respectively, in women.

4. Discussion

In the prospective Heinz Nixdorf Recall Study, previously known diabetes with poor glycemic control (indicated by HbA1c ≥ 7.0%) was strongly associated with ABI decrease and incident PAD over a 5-year and 10-year follow-up. For prediabetes and newly detected diabetes (indicated by HbA1c 5.7–6.4, and HbA1c ≥ 6.5%, respectively, in persons without previously known diabetes), and for well-controlled, previously known diabetes (indicated by HbA1c < 7.0%), barely any associations with ABI decrease or incident PAD were observed. Moreover, the incidence of Mönckeberg disease (defined by ABI > 1.4) was very low in subjects with diabetes at baseline.

4.1. Patients with previously known diabetes

In patients with previously known diabetes, all our analyses showed that ABI decrease is much less pronounced in well-controlled than in poorly controlled diabetes. This result supports recommendations by the American Diabetes Association (ADA) on standards of medical care in diabetes [28]. The ADA suggests a goal of HbA1c < 7.0% for most adults with diabetes. Only for patients with long life expectance, short diabetes duration and no advanced microvascular and macrovascular complications, an even lower target of HbA1c < 6.5% is suggested. For patients in a poor condition, with short life expectancy, history of hypoglycemia or advanced microvascular or macrovascular complications, less severe HbA1c targets (< 8.5%) are suggested.

Our study is in line with recent results from the ARIC study in which adjusted hazard ratios were 6.00 (95% CI: 3.73–9.66) and 1.74 (95% CI: 0.94–3.22), respectively, for poorly and well-controlled previously known diabetes (outcome: hospitalization with PAD diagnosis, reference: no diagnosed diabetes with HbA1c < 5.7%) [19]. There are a few further earlier prospective studies on the association between HbA1c and ABI. However, in these studies the new HbA1c based cut-offs for glycemic targets and for diagnosis of diabetes were not used. In a study of 82 Asian diabetes patients with a mean follow-up of 27.6 months, Hoe et al. found that a 1% increase in HbA1c was associated with an ABI decrease > 0.1 (HR = 1.47, 95%: 1.10–1.97) [17]. Earlier results from the ARIC study with a mean follow-up of 9.8 years showed that diabetes patients with HbA1c ≥ 7.5% were at a larger risk of incident ABI < 0.9 than diabetes patients with HbA1c < 6.0% (RR = 1.64, 95% CI: 0.94–2.87) [16]. With cross-sectional data from the NHANES study, Muntner et al. found about equal associations of poorly and well-controlled diabetes with prevalent PAD (defined by ABI < 0.9) (odds ratios = 2.33 (95% CI: 1.15–4.70), and 2.74 (95% CI: 1.25–6.02), respectively, for patients with diabetes and HbA1c ≥ 7.0%/ < 7.0%, *versus* those without diabetes and HbA1c < 5.3%) [29].

The comparability of the aforementioned studies on HbA1c and ABI with our study is compromised by the use of different measurement methods for ABI, e.g., Muntner et al. measured blood pressure only on the right brachial artery [29], and in the ARIC study, blood pressure was measured using an oscillometric device instead of standard Doppler technique [16]. In the recent study by Ding et al. the outcome was hospitalization because of incident PAD [19], which may also be due to microangiopathy, in particular in patients with critical limb ischemia (CLI) [30].

Contrary to earlier findings [31], we could not confirm that diabetes is a risk factor for Mönckeberg disease (defined by ABI > 1.4). Even in poorly controlled diabetes, only one out of 76 persons developed MD during follow-up. Thus, from our data, poorly controlled diabetes is a

Table 3
Odds ratios (95% confidence intervals) for the associations between HbA1c categories and incidence of ABI < 0.9 at 5-year and 10-year follow-up.

Previously known diabetes	HbA1c (%)	OR (95% CI) for 5-year follow-up				OR (95% CI) for 10-year follow-up			
		N	n	Model 1	Model 2	N	n	Model 1	Model 2
Yes	≥7.0	76	9 (11.8%)	4.3 (2.1–9.2)	3.5 (1.6–7.9)	44	10 (22.7%)	4.6 (2.2–9.7)	3.1 (1.3–7.0)
Yes	< 7.0	116	5 (4.3%)	1.5 (0.6–3.9)	1.5 (0.6–3.9)	65	4 (6.2%)	1.1 (0.4–3.1)	0.9 (0.3–2.7)
No	≥6.5	96	3 (3.1%)	1.1 (0.3–3.5)	0.8 (0.3–2.8)	57	2 (3.5%)	0.6 (0.1–2.3)	0.4 (0.1–1.7)
No	5.7–6.4	596	31 (5.2%)	1.8 (1.2–2.9)	1.6 (1.0–2.5)	421	40 (9.5%)	1.6 (1.1–2.4)	1.4 (0.9–2.1)
No	< 5.7 (ref)	2274	61 (2.7%)	1	1	1744	93 (5.3%)	1	1

Model 1: adjusted for age and sex.
Model 2: adjusted for age, sex, BMI, smoking, physical activity, systolic blood pressure, diastolic blood pressure, triglycerides, HDL cholesterol, LDL cholesterol, intake of statins, intake of antihypertensive medication.

risk factor for ABI decrease and for PAD, not for MD.

In sex-stratified analyses, the decline of ABI in poorly controlled diabetes was somewhat stronger in women than men. Due to the small number of subjects in the sex-specific strata, this result needs confirmation from further studies.

4.2. Patients with prediabetes or newly detected diabetes

In patients with prediabetes (HbA1c 5.7–6.4%) or newly detected diabetes (HbA1c ≥ 6.5%), barely any associations with ABI decrease or incident PAD were found in our study. Several explanations why ABI decline is not stronger in newly detected diabetes (HbA1c ≥ 6.5%) than in non-diabetic persons are conceivable.

First, in Germany, disease management programs were introduced in 2003, and strong improvements of diabetes care were observed by the National Health Surveys in the period of our study [32]. Moreover, the aims of the St Vincent declaration have at least partly been achieved in Germany: e.g., there was a stronger decrease of the risks of lower foot amputation and stroke in the diabetic than non-diabetic population [33,34]. Thus, improved diabetes care may be a reason why we did not observe ABI decline in newly detected diabetes.

Second, HbA1c is mainly associated with microvascular associations; the 6.5% cut-off for diagnosis of diabetes by HbA1c is largely based on studies which assessed associations between HbA1c and prevalence of retinopathy and found a somewhat sharp inflection point for HbA1c values of about 6.5% [35]. ABI, however, is mainly related to macrovascular complications like myocardial infarction, stroke or PAD. So the HbA1c 6.5% cut-off may be more sensitive for microvascular than macrovascular complications and their precursors.

Associations between prediabetes and ABI were rarely examined. In the Cardiovascular Health Study, baseline diabetes, but not impaired fasting glucose, was associated with ABI decline, which is in line with our study where HbA1c in the prediabetic range (5.7–6.4%) was not associated with ABI [37].

In recent analyses of ARIC data, associations of prediabetes and newly detected diabetes with hospitalization due to PAD diagnosis were observed (HR = 1.56, 95% CI: 1.17–2.06, and HR = 3.53, 95% CI: 2.39–5.22, respectively, compared to no diabetes and HbA1c < 5.7%) [19]. There are two explanations why these results differed from our results: first, the mean follow-up in the ARIC study was 20.7 years compared to 10 years in the HNR study. Second, as mentioned already above, in the ARIC study, hospitalization due to PAD was used as the outcome, which is a more severe endpoint than ABI < 0.9 and includes cases of critical limb ischemia in the development of which microvascular processes play a larger role [30].

In the HNR study, we have recently assessed associations between HbA1c in subjects with and without known diabetes and progression of coronary artery calcification, which is another measure of subclinical atherosclerosis [4]. Interestingly, results for ABI decrease and CAC progression were alike, i.e., we found associations with poorly controlled diabetes, but not with well-controlled or newly detected diabetes. Both results suggest that meeting the HbA1c 7.0% goal in diabetes might help delay atherosclerotic processes.

In addition to diabetes, further components of the metabolic syndrome are associated with ABI. In several cross-sectional and longitudinal studies, positive associations between hypertension and dyslipidemia and low ABI were reported [36–39]. Accordingly, in some prospective studies, patients with metabolic syndrome (mostly defined by NCEP ATP III criteria) were found to be at higher risk of developing peripheral arterial disease [40–42]. Thus, to avoid or delay ABI decline, prevention should not focus on diabetes alone, but also on other components of the metabolic syndrome.

4.3. Strengths and limitations

Strengths of our study are its population-based study group, its prospective design with extensive phenotyping of participants, and measurement of ABI at three points in time. One limitation of our study is the rather small number of patients with diabetes at baseline: in total, 288 patients had either newly detected or previously known diabetes at the first visit to the study center. Finally, even a 10-year follow-up might be insufficient to observe higher risks of ABI decrease in subjects with prediabetes or newly detected diabetes.

4.4. Conclusions

Our study confirms the ADA recommendation of meeting a 7.0% target goal in most adults with diabetes. Meeting this goal might help prevent PAD in subjects with diabetes, which is important considering that subjects with PAD and diabetes have a particularly poor prognosis.

Conflict of interest

The authors declared they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

Author contributions

Study concept and design: R.E., A.S., S.M.; Acquisition of data: R.E., K.K., A.S., S.M.; Analysis of data: B.K., N.L.; Drafting of the manuscript: B.K.; all authors reviewed and edited the manuscript.

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