Published in final edited form as:
Diabetes Care. 2007 October ; 30(10): 2646–2648. doi:10.2337/dc07-0517.

Intensive Treatment of Diabetes Is Associated With a Reduced Rate of Peripheral Arterial Calcification in The Diabetes Control and Complications Trial

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Peripheral arterial disease (PAD) is a significant contributor to the morbidity and mortality of >2 million Americans (1). In addition to its own specific disease risks, PAD has been shown to be a predictor of cardiovascular mortality and coronary artery disease, as well as a general marker for the atherosclerotic disease process (2,3). PAD complications, especially in the lower limb, are significantly greater in individuals with diabetes compared with those without diabetes, and the risk imparted by diabetes is similar or greater in magnitude to that seen for ischemic heart disease and stroke (4,5).

The aortofemoral arteries are prime sites for PAD; hence, determination of claudication and measurement of blood flow in the lower extremities are the most common assessments (6). A relatively low ankle systolic blood pressure (ankle-to-brachial ratio index [ABI]) has been found to be an indicator of atherosclerosis/occlusion in this region (5). Conversely, in diabetes, a high-pressure ABI due to medial wall arterial calcification and non-compressible vessels may also be associated with adverse outcomes, including diabetic kidney disease (7). Sex differences have been reported in ABI measurements in type 1 diabetes, with women having a greater frequency of low ABI and men having a higher frequency of high ABI (7). Here, we extend these analyses by examining the effect of previous intensive diabetes management on the development of abnormally high and low ABIs in the Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) cohort with the hypothesis that intensive diabetes management will be protective against both high and low ABIs.

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A table elsewhere in this issue shows conventional and Syste`me International (SI) units and conversion factors for many substances.

RESEARCH AND DESIGN METHODS

Between 1983 and 1989, the DCCT enrolled 1,441 subjects with type 1 diabetes who, at baseline, were aged 13–39 years, had diabetes duration for 1–15 years, and were in generally good health (8). At the end of the DCCT in 1993, after 6.5 years of mean follow-up, intensive therapy (9) was recommended for all subjects, and they returned to their own health care providers for diabetes care. In 1994, >95% of the 1,425 surviving members volunteered to participate in the EDIC observational follow-up study (10).

ABI by Doppler

ABI was measured at each annual follow-up visit using an appropriately sized blood pressure cuff, a Doppler stethoscope, and acoustic gel. Participants were assessed in the supine position after resting for at least 5 min without any stressful stimuli. The order of the measurements was the right dorsalis pedis, the right posterior tibial, and the right arm pressure at the antecubital fossa. These three sites were measured by the same order on the left, yielding six measurements in total.

Other procedures

Each EDIC subject had an annual history, physical examination, electrocardiogram, and laboratory testing, including serum creatinine and A1C, determined in the same manner as during the DCCT (10). Fasting lipid profiles and 4-h urine collections for measurement of albumin excretion rate and creatinine clearance were obtained in alternate years during EDIC.

Outcome definitions

The four systolic ankle pressures were divided by the mean of the two brachial pressures to yield four values for ABI. The ABI selected for the analysis was the smallest of the four ratios in accordance with the EDIC manual of operations. The computed ABI values were then dichotomized according to the following definitions representing two measures of occlusion and one marker for calcification. For occlusion, thresholds of <0.90 and <0.80 were considered to represent early onset (11,12) and clinically relevant occlusion (7,13), respectively. Calcification of peripheral arteries was defined as an ABI that exceeded 1.3 (12). For each end point definition, the age when the event first occurred was computed for analysis. For participants not developing an outcome, the last reported age was used (i.e., a censored observation).

Statistical analysis

Unadjusted Cox models were constructed to examine the relationship of the DCCT treatment with each outcome separately. These models were supplemented by models that adjusted for known biological risk factors and tested for a DCCT treatment-by-sex interaction. The risk factors considered included baseline predictors of diabetes duration, sex, and mild retinopathy at DCCT randomization and time-varying covariates of systolic blood pressure, A1C, LDL, and the Modification of Diet in Renal Disease Study glomular fitration rate (14). The type I error rate was determined to be 0.05 a priori, and no correction for multiple comparisons was applied to reported *P* values.

RESULTS

A total of 1,398 (730 male and 668 female) subjects were studied over the course of 12 years, and 637 (45.6%) and 233 (16.7%) of the participants developed a low ABI (<0.9) or a clinically relevant (<0.8) level of occlusion, respectively. Similarly, 215 participants (15.4%) developed arterial calcification as denoted by ABI >1.3. In unadjusted analyses (Table 1), no effect of

previous DCCT intensive treatment was seen for either low or clinically relevant occlusion ($P = 0.41$ and 0.73, respectively). Prior intensive treatment, however, was protective for arterial calcification (hazard ratio [HR] 0.72 [95% CI 0.55–0.94], $P = 0.02$), with 94 events in the original intensive group and 121 events in the conventional treatment group.

In 1,018 nonsmokers and after adjustment for the biological risk factors, the effect of intensive treatment remained not statistically significant for both measures of occlusion. The effect of treatment on arterial calcification remained significant (HR 0.69 [95% CI 0.50–0.95], $P = 0.02$) after adjustment. Consistent with a previous study in type 1 diabetes (7), men were more likely to develop arterial calcification (HR 2.2, $P < 0.01$), whereas women were more likely to develop mild occlusion (ABI<0.9, HR 0.58, $P < 0.01$).

CONCLUSIONS

This report suggests that intensive, compared with conventional, therapy administered during the DCCT may be protective for peripheral arterial calcification, consistent with the previous coronary calcification findings on this same cohort (15). The magnitude of the effect remained stable after adjustment for other risk factors. The lack of an effect of intensive diabetes therapy on peripheral arterial occlusion seems surprising, given the clear benefit seen in the DCCT/EDIC on coronary occlusive events (16). It is likely, however, that some participants with occlusion, and thus an expected low ABI, may also have calcification. The increased rigidity of the artery, resulting in a “falsely” high pressure, may obscure underlying occlusion (13). Such misclassification may occur more frequently in the conventional group (given the tendency of this group to have more calcification), leading to a reduction in the ability to detect treatment group differences. Additional studies are needed to assess the factors associated with these risk differences and to better delineate differences in the risk factors for peripheral vascular disease and coronary disease in this type 1 diabetic cohort. This study’s results provide further support for the use of intensive glycemic control to improve peripheral vascular health.

Abbreviations

ABI, ankle-to-brachial ratio index; DCCT, Diabetes Control and Complications Trial; EDIC, Epidemiology of Diabetes Interventions and Complications; PAD, peripheral arterial disease.

Acknowledgments

The DCCT/EDIC was sponsored through research contracts from the Division of Diabetes, Endocrinology and Metabolic Diseases of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), National Institutes of Health. Additional support was provided by the General Clinical Research Centers Program, the National Center for Research Resources, the National Institutes of Health, and by Genentech through a Cooperative Research and Development Agreement with the NIDDK.

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Table 1

HR estimates for the development of PAD in type 1 diabetes

	ABI <0.9 (occlusion)		ABI <0.8 (clinically significant occlusion)		ABI >1.3 (calcification)	
Parameter*	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***
Single predictor models (unadjusted)						
Intensive treatment†	0.936 (0.79–1.095)	0.406	0.955 (0.737–1.238)	0.728	0.717 (0.547–0.940)	0.016
Male sex†	0.616 (0.527–0.722)	<0.001	0.723 (0.558–0.938)	0.014	1.854 (1.391–2.470)	<0.001
Duration	1.000 (0.999–1.002)	0.740	1.000 (0.998–1.002)	0.866	1.000 (0.998–1.002)	0.971
Systolic blood pressure	0.998 (0.993–1.004)	0.586	0.998 (0.989–1.007)	0.672	0.997 (0.987–1.007)	0.495
A1C	1.074 (1.017–1.133)	0.010	1.092 (0.998–1.196)	0.055	0.955 (0.866–1.054)	0.363
LDL cholesterol	0.997 (0.994–1.000)	0.036	0.996 (0.991–1.000)	0.071	1.002 (0.997–1.006)	0.484
Non–HDL cholesterol	0.999 (0.996–1.001)	0.230	0.998 (0.995–1.002)	0.428	1.001 (0.998–1.005)	0.466
Total cholesterol	0.999 (0.997–1.001)	0.376	1.000 (0.996–1.004)	0.886	1.001 (0.997–1.005)	0.619
GFR	1.008 (1.003–1.013)	0.001	1.002 (0.994–1.010)	0.566	1.003 (0.995–1.012)	0.409
Ever smoker	1.531 (1.297–1.807)	<0.001	1.702 (1.303–2.224)	<0.001	0.736 (0.531–1.020)	0.066
Retinopathy at baseline	0.978 (0.836–1.144)	0.785	1.185 (0.914–1.53)	0.200	1.022 (0.781–1.336)	0.876
Model 2 (adjusted)‡§						
Intensive treatment†	0.955 (0.775–1.178)	0.670	1.033 (0.731–1.461)	0.853	0.676 (0.489–0.934)	0.018
Duration	1.000 (0.997–1.003)	0.997	1.003 (0.998–1.008)	0.277	1.001 (0.996–1.005)	0.784
Systolic blood pressure	1.006 (0.998–1.013)	0.129	0.994 (0.982–1.007)	0.383	0.997 (0.986–1.009)	0.663
A1C	1.049 (0.971–1.133)	0.228	1.114 (0.982–1.264)	0.093	0.973 (0.857–1.106)	0.676
LDL	1.000 (0.996–1.003)	0.883	0.996 (0.989–1.002)	0.178	1.002 (0.996–1.007)	0.508
GFR	1.005 (0.999–1.012)	0.124	0.991 (0.980–1.002)	0.117	1.001 (0.991–1.012)	0.783
Male sex†	0.578 (0.464–0.720)	<0.001	0.911 (0.635–1.306)	0.611	2.203 (1.539–3.155)	<0.001
Retinopathy at baseline	0.846 (0.616–1.163)	0.304	1.041 (0.605–1.790)	0.885	1.134 (0.705–1.825)	0.603

n = 1,398. Data were estimated using SAS (version 9/10/3; SAS, Cary, NC).

*All biological parameters were modeled as time-dependent covariates.

†The reported HRs are for intensive treatment during the DCCT relative to standard therapy during DCCT and for male relative to female subjects.

‡Sex by DCCT treatment interactions not statistically significant were at an $\alpha = 0.15$ level of significance.

[§] Tested only for nonsmokers (n = 1,018).