Arterial Wall Elastic Properties and Endothelial Dysfunction in the Diabetic Foot Syndrome in Patients With Type 2 Diabetes

DOI: 10.2337/dc15-1042

Diabetic foot (DF) syndrome is the most common lower-extremity complication of poorly controlled type 2 diabetes (T2D) (1). DF affects the quality of life of T2D patients and is associated with increased morbidity (2). T2D-related mechanisms induce endothelial dysfunction and adverse effects on vascular biology (3). We have recently shown that measurements of endothelial function and arterial stiffness are strongly associated with diabetic retinopathy (4), but their association with DF has not been explored yet.

To examine this, we enrolled 284 consecutive T2D subjects visiting our outpatient diabetes clinic and 196 age- and sex-matched healthy control subjects without evidence of diabetes or cardiovascular or other disease. Subjects with known malignancy, hepatic impairment, or acute or chronic inflammatory disease were excluded from the study. Study protocol was approved by the institutional ethics committee. Endothelial function was assessed by the flow-mediated dilation (FMD) of the brachial artery and carotid-femoral pulse wave velocity (PWV) and augmentation index (AIx) were assessed by SphygmoCor (AtCor Medical) as previously described (4).

Prevalence of DF was 24.6% among T2D patients. There were no significant differences in age, sex, cardiovascular risk factors (such as smoking, hypertension, and hyperlipidemia), and HbA1c% between T2D with DF and no DF (NDF) (P = NS for all). However, DF patients had significantly increased T2D duration compared with NDF patients (19.5 ± 1.1 vs. 12.0 ± 0.6 years, P = 0.001). As expected, T2D was associated with lower FMD and increased PWV and AIx compared with subjects without diabetes, while DF was associated with further adverse effects on endothelial function and arterial stiffness within the group of T2D patients (Fig. 1A–C). Staging of DF (according to the University of Texas diabetic wound classification system) was significantly associated with log[FMD] (β = −0.165, P = 0.006), AIx (β = 0.200, P < 0.05), and log[PWV] (β = 0.234, P < 0.05), suggesting further exacerbation of endothelial dysfunction and arterial stiffening with increasing severity of DF syndrome. Interestingly, T2D duration was positively associated with both PWV and AIx but only modestly with FMD (Fig. 1D–F), suggesting that arterial stiffening is a gradual and ongoing process in patients with diabetes. On the other hand, log[HbA1c%] was not associated with FMD, PWV, or AIx (P = NS for all), suggesting that vascular dysfunction may not be reversible by strict glycemic control. In the multivariate logistic regression analysis, including as independent variables those that were associated with DF in bivariate analysis, the only independent predictors of DF were log[FMD] [Exp(β) = 0.174, 95% CI 0.031–0.981, P = 0.048] and AIx% [Exp(β) = 1.093, 95% CI 1.018–1.172, P = 0.014] (R² for the model = 0.167).

Peripheral neuropathy, impaired wound healing, local inflammation, and decreased nitric oxide bioavailability may all affect local microcirculation environment and contribute to DF (1). Herein, we provide the first evidence that DF in T2D is associated with endothelial dysfunction and increased stiffness of large arteries. We observed that endothelial dysfunction is installed at an early stage in the course of diabetes, while impairment of vascular elasticity is a gradual process in patients with diabetes. Our results show increasing arterial stiffness with T2D duration (independently of glycemic control), indicating an ongoing vascular stiffening, which is strongly associated with DF. Even though no data were collected on ankle-brachial index or direct blood flow measurements in lower extremities, our findings suggest that both...
brachial FMD and Aix are strongly and independently associated with DF. Further evidence is needed to clarify whether these widely used vascular function indices could have a role as screening tools for the risk stratification of T2D patients.

Acknowledgments. The authors thank all the faculty and staff of Division of Diabetes, First Department of Propaedeutic and Internal Medicine, Laiko Hospital, University of Athens Medical School, Athens, Greece.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

Figure 1—Associations between DF syndrome, endothelial function, and arterial stiffness indices. Patients with T2D and DF had increased PWV (A) and arterial reflected waves (Aix (B)) and lower brachial artery FMD (C) compared with either subjects with no T2D or NDF. Both PWV and Aix were strongly positively associated with T2D duration (D and E), while there was only a modest negative association between T2D duration and brachial FMD (F). *P < 0.001, **P < 0.0001 vs. control group; §P < 0.05, #P < 0.001 vs. NDF group. DM, diabetes; y, years.

References