PULSE PRESSURE AND PREDICTION OF INCIDENT FOOT ULCERS IN TYPE 2 DIABETES

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Objectives — To assess the relevance of pulse pressure (PP) as a predictor of foot ulcers in type 2 diabetes.

Research design and methods — A cohort study was performed on a consecutive series of 1,945 type 2 diabetic outpatients without foot ulcer at baseline. Incident foot ulcers were identified through the Regional Hospital Discharge system, which contains ICD codes of current diagnoses.

Results – During a mean follow-up of 4.2±2.2 years, 86 ulcers were observed. After adjusting for confounders, the highest quartiles of PP had a 2.39[1.14-5.02]-fold risk of foot ulcers. When ischemic ulcers were considered separately, the highest PP quartile was associated with an increased age- and sex-adjusted risk (2.08[1.02-4.24]), whereas no increase of risk was observed for neuropathic ulcers.

Conclusion — Elevated PP represents an independent predictor of foot ulcers in diabetic patients; this parameter should be considered for the stratification of risk of ischemic or neuroischemic ulcers.
Pulse pressure (PP) is a recognized risk factor for cardiovascular disease, in nondiabetic (1-4) as well as in diabetic subjects (5,6). In particular, elevated PP is associated with increased risk of arteriopathy of lower limbs, even after adjusting for mean blood pressure (7). This study is aimed at the assessment the relevance of PP as a predictor of foot ulcers in type 2 diabetes, which has not been specifically investigated so far.

RESEARCH DESIGN AND METHODS

A cohort study was performed on a consecutive series of 1,945 type 2 diabetic outpatients referred to the Diabetes Clinic Clinic of the Geriatric Unit of Careggi University Hospital in Florence between December 1st, 1995, and December 1st, 2000. Blood pressure was measured using a mercury sphygmomanometer, with a cuff of appropriate size, considering the mean of three measurements taken 5 minutes apart in sitting position. Serum cholesterol, HDL cholesterol, and triglyceride were measured, using an automated method (Aeroset, Abbott Laboratories), on blood samples drawn in the morning after overnight fast. Neuropathy was ascertained through biothesiometry (>25 V at toes) (8), and lower limb arteriopathy was screened through Ankle-Brachial Index (ABI<0.8) (9). HbA1c was determined with HPLC (Menarini Diagnostics, Florence, Italy; upper normal limit 5.8%). Comorbidity was assessed through the calculation of Charlson’s comorbidity score (CCS), which includes diabetes and its complications, cardiovascular disease, chronic skin ulcers, renal insufficiency, liver diseases, chronic obstructive pulmonary disease, malignancies, arthritis/arthritis, HIV-infections (10). PP was calculated as the difference between systolic and diastolic pressure.

Patients were observed until death, incidence of foot ulcer, or Dec 31st, 2005. Foot ulcers were identified through the Regional Hospital Discharge system, which contains ICD codes of current diagnoses (ICD codes 707 and/or 440.23); ulcers were considered ischemic when ICD code 440 or 250.7 was present, and neuropathic with codes 357 or 250.6. This method identified 40 (77%) of 52 consecutive cases of incident ulcers referred to our Clinic during 2004.

Chi-square test, Student’s unpaired and paired two-sided t test, and Mann-Whitney U test were used for comparisons whenever appropriate; Spearman’s method was used for correlations. Survival estimates were performed using Kaplan-Meier curves; stepwise Cox regression was used for multivariate analysis.

RESULTS

Patients enrolled (56.7% women) had a mean (±SD) age of 64.0±12.7 years, duration of diabetes 10.7±10.5 years, and HbA1c 8.1±1.9%. Of the 1945 patients, 50.3, 47.1, and 32.3% received treatment with metformin, insulin secretagogues, or insulin, respectively. The prevalence of neuropathy, arteriopathy of lower limbs, and retinopathy was 22.2, 10.1, and 8.8%, respectively. Systolic, diastolic, and pulse pressure was 142.4±20.1, 81.3±10.5, and 61.1±16.4 mmHg, respectively; 61.2, 51.6 and 31.1% were receiving anti-hypertensive treatment, antiaggregants, and statins, respectively.

Patients in the highest quartile (>70 mmHg) of PP had a significantly (p<0.01) higher age (70.5±8.6 vs
62.5±13.0 years), duration of diabetes (14.1±11.1 vs 10.0±10.2 years), CCS (2.5±1.5 vs 2.1±1.5), and prevalence of neuropathy (36.3 vs 19.2%), arteriopathy (10.9 vs 7.0%), retinopathy (13.0 vs 7.9%), microalbuminuria (16.8 vs 10.2%), and previous stroke (7.4 vs 3.5%); they also had a higher systolic (168 ±15 vs 136±16 mmHg), but not diastolic (82±11 vs 81±10 mmHg). No difference between patients in the highest PP quartile and the rest of the sample was observed for HbA1c, lipid profile, and BMI (data not shown). An inverse correlation was observed between PP and ABI (r=-0.27, p<0.01).

During a mean follow-up of 4.2±2.2 years, 86 ulcers were observed, with an yearly incidence rate of 1.1%. Of the incident ulcers, 38 were neuropathic, 15 ischemic, 20 neuro-ischemic, and 13 of other origin. Age was a relevant predictor of incident ulcers (1.05[1.03-1.07]; p<0.001). After adjusting for sex and age, other predictors included duration of diabetes (1.03[1.01-1.05]; p<0.001), HbA1c (1.20[1.10-1.32]; p<0.001), neuropathy (3.93[2.55-6.05]; p<0.001), arteriopathy of lower limbs (4.32[2.79-7.38]; p<0.001), retinopathy (1.97[1.13-3.43]; p=0.017), and previous foot ulcers (31.53[20.17-49.29]; p<0.001), but not cholesterol, microalbuminuria or renal failure (data not shown).

Elevated pulse pressure was associated with a significantly increased risk of foot ulcers (Fig. 1). After adjusting for age, sex, duration of diabetes, systolic blood pressure, and CCS, patients in the highest quartiles of PP had a 2.39[1.14-5.02]-fold risk of foot ulcers in comparison with the rest of the sample (p=0.022). When ischemic or neuroischemic ulcers were considered separately, the highest PP quartile was associated with a significantly increased age- and sex-adjusted risk (2.08[1.02-4.24]; p=0.043), whereas no increase of risk was observed for neuropathic ulcers (1.33[0.67-2.65]; p=0.42).

**DISCUSSION**

The present study shows for the first time that pulse pressure is a relevant, independent predictor of incident ischemic or neuroischemic foot ulcers in type 2 diabetic patients. The reduction of arterial compliance, which is revealed by the increase of PP, facilitates atherosclerotic lesions in different districts, including lower limbs (7). Impairment of insulin sensitivity, which has been reported to be associated with elevated PP (11), could contribute to micro- and macrovascular lesions responsible for foot ulcers. Furthermore, elevated PP is associated with lower ABI.

The knowledge of the association of elevated PP with foot ulcers is relevant for identification of patients at higher risk, to be referred to more accurate programs for screening of arteriopathy of lower limbs and to specific educational interventions. It should be considered that the risk of foot ulcers is more than doubled in patients in the highest quartile of PP; the increase of risk is comparable to that attributable to known neuropathy or arteriopathy of lower limbs.

Some limitations should be recognized. Register-based ascertainment of incident ulcers inevitably implies that minor lesions not requiring treatment in hospital-based Clinics are missed, thus leading to an underestimation, by at least 20%, of the actual incidence of this condition. The Register-based identification of ulcers, without no direct observation, does not allow any characterization of cases. Furthermore, PP was assessed only through office measurement, which are
less accurate than, although similarly predictive of cardiovascular events as, results of ambulatory monitoring (12).

In conclusion, elevated pulse pressure represents an independent predictor of foot ulcers in diabetic patients; this parameter should be considered for the stratification of risk of ischemic or neuroischemic ulcers.
REFERENCES


