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Short Report: Complications

Predictors of decrease in ankle–brachial index among patients with diabetes mellitus

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Running head: Predictors of decrease in ankle–brachial index • *J. Hoe et al.*

Abstract

Aim Screening for peripheral arterial disease, a complication among patients with diabetes, is performed by periodic assessment of ankle–brachial index. We aimed to study the degree of ankle–brachial index change over time and factors associated with significant change.

Method We assessed difference between two ankle–brachial index measurements over time in a consecutive series of 82 patients with Type 2 diabetes. All patients had ankle–brachial index > 0.9 but ≤ 1.3 for the first measurement, and significant ankle–brachial index decrease was defined as a decrease of > 0.1 in the follow-up measurement compared with the baseline.

Results The mean follow-up duration was 27.6 (median 30.0) months. Significant ankle–brachial index decrease was seen in 20.7% of patients, including 5% with follow-up ankle–brachial index of ≤ 0.9, consistent with the diagnosis of peripheral arterial disease. After adjusting for age and gender, higher baseline HbA_{1c} and serum creatinine levels, increase in follow-up serum LDL cholesterol levels compared with baseline and history of retinopathy were predictors of significant ankle–brachial index decrease.

Conclusions Our study suggests that, within two years, one in five patients with diabetes and a normal ankle–brachial index may have significant progression of peripheral arterial disease. Annual ankle–brachial index assessment and better control of hyperlipidaemia may thus be required for at-risk patients with poor glycaemic control, renal impairment and retinopathy.

Keywords ankle–brachial index, diabetes, peripheral artery disease, progression

Introduction

Peripheral arterial disease in patients with diabetes is a risk factor for lower extremity amputation, coronary heart disease and stroke [1,2]. As patients may remain asymptomatic until late in the disease [3,4] or may present with atypical symptoms [5], screening for peripheral arterial disease is important. The ankle–brachial index is a reproducible, non-invasive index used to screen and detect peripheral arterial disease [6]. The sensitivity and specificity of ankle–brachial index for angiographically defined peripheral arterial disease has been reported to be 90 and 95%, respectively [7]. The American Diabetes Association recommends measuring ankle–brachial index for asymptomatic patients older than 50 years of age, and for younger patients with diabetes or other vascular risk factors, and repeating the measurement 5 yearly if the first result is normal [6]. However, data on trends of ankle–brachial index change in patients with diabetes are limited. This study explored the change in two readings of ankle–brachial index over a mean duration of 27.6 months in patients with diabetes and investigates the factors associated with significant ankle–brachial index decrease.

Materials and methods

Study population

The study population was a consecutive series of patients who had a baseline ankle–brachial index assessment performed at the Diabetes Centre, a tertiary referral centre for management of diabetes, in April–June 2007, and a follow-up ankle–brachial index assessment between April 2008 and May 2011. After excluding all patients with known complications of peripheral arterial disease and raised serum creatinine levels at baseline assessment, and whose baseline ankle–brachial index reading was abnormal (≤ 0.9 or > 1.3), there were 87 patients who had two ankle–brachial index assessments each. Five patients whose follow-up ankle–brachial index was > 1.3 were further excluded, and the remaining 82 patients constituted the population for this study.

Ethical approval

Ethics approval was obtained from the National Healthcare Group Institutional Review Board prior to study commencement. Written informed consent was obtained from all participants before conduct of study.

Measurement of ankle–brachial index

Ankle and toe pressures were measured by Doppler ultrasound and photophlethysmography, respectively, using a standardized Doppler ultrasonic device (8 MHz; Smartdop TM 20EX, bidirectional blood flow detector; Hadeco, XXXX, Japan). Brachial pressure was measured using an automated blood pressure monitor (Dinamap Pro100V2; Criticon, Norderstedt, Germany). Measurements were carried out after a 5-min rest in the supine position by trained technicians. Ankle–brachial index was calculated as the ratio of the higher of the two systolic pressures (from posterior tibial and dorsalis pedis) at the ankle to the average of the right and left brachial artery pressures. The lower reading between the two ankle–brachial index readings of each patient was taken as the ankle–brachial index reading of that patient.

Peripheral arterial disease was defined as having a resting ankle–brachial index of ≤ 0.9 [9]. Significant ankle–brachial index decrease was defined as a decrease in ankle–brachial index of more than 0.1 in the follow-up reading compared with baseline [9]. These criteria exceeded the measurement variability of ankle–

brachial index in our institution, where the intra-observer variation was 7.6% and the inter-observer variation was 12.8%.

Other clinical and biochemical factors

Hypertension was defined as systolic blood pressure > 140 mmHg or diastolic blood pressure > 90 mmHg, or by self-reported history of hypertension. Coronary heart disease was defined by a self-reported history or medical record of ’blockade of arteries to the heart‘, ’heart attack‘, ’balloon angioplasty of coronary artery‘, ’heart bypass operation‘, ’ischaemic heart disease‘ or ’coronary heart disease‘. Stroke was defined by a self-report or medical record of stroke. Retinopathy was defined by medical record of microaneurysms, dot and blot haemorrhages, hard exudates, proliferative changes or maculopathy noted by an endocrinologist or ophthalmologist.

All patients had HbA_{1c}, serum creatinine and lipids, and urine albumin:creatinine ratio measured in our institution’s reference laboratory at both visits for baseline and follow-up ankle–brachial index assessments using an automatized autoanalyser (Roche Cobas Integra 700; XXXXX, XXXXX, XXXXX). Plasma glucose was obtained by enzymatic methods using blood collected in fluoride oxalate tubes.

Statistical analysis

Person-months were computed from date of baseline ankle–brachial index assessment to follow-up assessment. All potential risk factors were analysed either as binary traits for categorical variables or linear traits for continuous variables. Proportional hazards (Cox) regression methods were used to examine the associations between the various risk factors and significant ankle–brachial index decrease with adjustment for age and gender. All analyses were performed in SPSS version 19 (SPSS Inc., Chicago, IL, USA). All statistical tests were two-sided with a level of significance defined as a *P*-value < 0.05.

Results

Among the 82 patients, 42 (51.2%) were men, with Chinese as the majority (n = 61, 74.4%). The mean age was 54.9 years (SD 13.0, range 20–84 years) and mean duration of diabetes was 8.8 years (SD 7.4 years, range 1 month to 40 years). The mean HbA_{1c} was 61 mmol/mol (range 38–127 mmol/mol) [7.7% (range 5.6–13.8%)]. The majority of patients had a history of hypertension (52.4%) and hypercholesterolaemia (69.5%). Approximately 15.9% were current smokers, 14.6% had a history of ischaemic heart disease and 4.9% had cerebrovascular disease. Mean follow-up duration was 27.6 months (SD 13.1, range 9–48 months, median 30.0 months).

A total of 46 (56%) patients had decrease in the follow-up ankle–brachial index reading and, among them, 17 (20.7%) had a decrease of > 0.1, which was defined as significant ankle–brachial index decrease. Four patients (5%) were diagnosed to have peripheral arterial disease as their second ankle–brachial index readings were ≤ 0.9.

Compared with those without significant decrease, patients with significant ankle–brachial index decrease were more likely to be older, have higher HbA_{1c} and serum creatinine at baseline visit, and were more likely to have retinopathy. These patients also had a mean increase of 0.068 mmol/l in follow-up LDL, while the patients without significant ankle–brachial index decrease lowered their serum LDL by a mean of 0.197 mmol/l.

After adjusting for age and gender, the risk of having significant ankle–brachial index decline increased with increasing HbA_{1c} and creatinine level at baseline. The risk also increased with increasing positive difference in follow-up serum LDL compared with baseline. Presence of retinopathy was also a significant predictor of ankle–brachial index decrease (Table 1).

Discussion

In this follow-up study on patients with diabetes who had normal ankle–brachial index at baseline, approximately one-fifth had a significant decrease in ankle–brachial index > 0.1. This incidence of significant ankle–brachial index decrease was higher than previous reports [10,11]. The mean decrease in ankle–brachial index in this study was 0.04 per year, and this was also substantially higher than that seen in the general population [10,12], thus underscoring the importance of diabetes as a risk factor for progression of peripheral arterial disease [11,13].

Concurring with an earlier cross-sectional study [14], patients who had a significant ankle–brachial index decrease in this study had higher serum creatinine levels at baseline. Impaired renal function is known to be associated with atherosclerosis and cardiovascular events [15], although the biological pathway linking the association between reduced renal function and arterial narrowing is not fully elucidated. In addition to both diseases sharing common risk factors, it is possible that metabolic changes caused by decreased renal function can lead directly to atherosclerotic disease and subsequent decline in ankle–brachial index.

Our data show that the smaller the decrease in serum LDL level at follow-up compared with baseline, the higher the risk was for significant ankle–brachial index decrease. This provides evidence for the importance of high LDL as a major atherosclerotic risk factor and emphasizes the importance of intensive LDL lowering in patients who are at high risk of atherosclerotic disease [16,17].

Retinopathy is an important microvascular complication in patients with diabetes and previous studies have observed the association between retinopathy and risk of lower limb amputations [18]. Our finding of retinopathy as an independent predictor of significant decrease in ankle–brachial index suggests that patients with retinopathy should have ankle–brachial index measurements carried out regularly for the diagnosis of peripheral arterial disease. Our study also shows that increasing HbA_{1c} is related to progression of peripheral arterial disease and provides evidence for poor glycaemic control as a risk factor for cardiovascular disease [19] and lower limb amputation [20].

The strength of this study is that it is one of the few studies to have prospective follow-up of ankle–brachial index measurements in a well-defined population of patients undergoing management for diabetes in a tertiary referral centre. The limitations of our study include a small sample size, as we excluded patients who had baseline ankle–brachial index measurements carried out at the centre, but did not return for follow-up assessment because of the relocation of our institution from western to northern Singapore. Nevertheless, compared with these patients who were excluded, except for a lower prevalence of retinopathy (15.8 vs. 28.9%) at baseline in patients included in this study, both groups were similar in age, duration of diabetes, baseline HbA_{1c} level, and the prevalence of hypertension, hyperlipidaemia, coronary heart disease and stroke. While smoking is an established predictor of ankle–brachial index decline [21], we were unable to demonstrate this association because of the small number of smokers in our study population.

In conclusion, our results suggest that, within 2 years, 20% of patients with diabetes and normal ankle–brachial index might have a significant decrease in ankle–brachial index, with 5% progressing to peripheral arterial disease, suggesting that repeat ankle–brachial index measurements should be carried out annually for patients with diabetes. Patients at risk of peripheral arterial disease will benefit from good control of hyperglycaemia and hyperlipidaemia and from regular screening using ankle–brachial index assessment.

Competing interests

Nothing to declare.

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Table 1 Association between factors and significant ankle–brachial index decrease

Variable	Hazard ratio (95% CI)	*P*-value
Smoking		
Non-smoker	1.00	
Smoker	0.34 (0.04–2.64)	0.300
Per unit increase in duration of diabetes (years)	1.00 (0.99–1.01)	0.715
Per unit increase in baseline HbA_{1c} (%)	1.47 (1.10–1.97)	0.009
Per unit increase in baseline systolic blood pressure (mmHg)	1.01 (0.96–1.05)	0.769
Per unit increase in baseline diastolic blood pressure (mmHg)	0.99 (0.93–1.06)	0.868
Per unit increase in BMI (kg/m^2)	1.02 (0.93–1.11)	0.672
Per unit increase in baseline creatinine (μmol/l)	1.02 (1.00–1.04)	0.038
Per unit increase in baseline HDL (mmol/l)	0.95 (0.17–5.47)	0.955
Per unit increase in baseline LDL (mmol/l)	1.03 (0.50–2.13)	0.943
Per unit increase in follow-up LDL from baseline (mmol/l)	1.89 (1.00–3.55)	0.050
History of hypertension		
No	1.00	
Yes	0.63 (0.20–1.91)	0.410
Coronary heart disease		
No	1.00	
Yes	0.87 (0.17–4.33)	0.859
Cerebrovascular disease		
No	1.00	
Yes	4.75 (0.82–27.5)	0.081
Retinopathy		
No	1.00	
Yes	3.93 (1.15–13.4)	0.029

Adjusted for age (years) and gender.