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Shared and additional risk factors for decrease of toe-brachial index compared to ankle-brachial index in Japanese patients with diabetes mellitus

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ABSTRACT

Objective: Some diabetic patients have a low toe-brachial index (TBI) despite their normal ankle-brachial index (ABI). We statistically investigated whether the impact of risk factors on TBI would be different compared to ABI.
Research design and methods: We used a database of 1738 limbs of consecutive 869 Japanese diabetic patients whose ABI and TBI were simultaneously evaluated. We developed a common regression model to ABI and TBI by extending the linear mixed model, and statistically detected the difference in the impact of risk factors between the two indices.
Results: Sex, smoking, proteinuria, hypertension, and history of stroke and coronary artery disease were common independent risk factors for the decrease of ABI and TBI; their impacts on ABI and TBI were not significantly different. On the other hand, the impact of age, diabetic duration, and body mass index was significantly different between the two indices (all $p < 0.05$). Age and body mass index were significantly associated with TBI but not with ABI. Diabetic duration had a significant impact both on TBI and ABI, but the impact on TBI was significantly greater than that on ABI ($\beta = -0.144$ vs. -0.087; $p < 0.05$). In the population with normal ABI, patients with these risk factors had a higher prevalence of decreased TBI.
Conclusions: The risk factors for the decrease of ABI and TBI were not identical in Japanese diabetic patients. Age, diabetic duration and body mass index were associated with reduced TBI in patients with normal ABI.

1. Introduction

Peripheral arterial disease (PAD) is one of the major complications in diabetic patients [1,2]. Patients with PAD are at high risk not only for an unfavorable limb prognosis including lower extremity amputation, but also for future cardiovascular events [3,4]. Many patients with PAD are asymptomatic and therefore its screening is important in clinical practice. Most familiar non-invasive screening tools for PAD are so far ankle-brachial index (ABI) and toe-brachial index (TBI) [5,6]. Both indices reflect arterial hemodynamics in lower extremity, and a reduced value of these indices indicates hemodynamically-significant arterial stenosis, i.e., the presence of PAD.

However, in clinical settings, the two findings do not always agree with each other [7,8]. Some patients have a normal ABI but a reduced TBI, whereas both ABI and TBI are decreased in other patients. It is expected that this would come from the difference in patients' clinical backgrounds. Indeed, previous studies suggested that the risk factors associated with the decrease of ABI and TBI were not identical [9]. However, those studies assessed the association of clinical factors with ABI and TBI separately and did not directly compare the impact of risk factors between ABI and TBI. It remained unclear whether there was any significant difference in the impact of risk factors between the two indices, and which risk factors would more strongly influence one index than the other.

In the current study, we developed a common regression model to ABI and TBI by extending the linear mixed model, and statistically investigated whether the impact of risk factors would be different between the decrease of ABI and TBI in Japanese patients with diabetes mellitus.

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2. Research design and methods

2.1. Study population and definitions

We used a retrospective clinical database of 1738 limbs of 869 Japanese diabetic patients whose ABI and TBI were simultaneously evaluated in Osaka University Hospital, Suita, Japan, between 2004 and 2012. The study was in accordance with Ethical Guidelines for Epidemiological Research in Japan and was approved by the human ethics committee of Osaka University. ABI and TBI were assessed by one trained certified diabetes educator with the use of an automated oscillometric device (form ABI/PWV, Omron Healthcare, Co., Ltd., Kyoto, Japan). When the reproducibility of the ABI and TBI measurements was assessed in 20 limbs of 10 Japanese diabetic patients, the absolute intra-individual difference was 0.01 ± 0.05 in ABI and -0.02 ± 0.09 in TBI. The intra-class correlation coefficient was calculated to be 0.90 [95% confidence interval (CI): 0.75–0.96] in ABI and 0.89 [95% CI: 0.74 to 0.95] in TBI, respectively. The database was consecutively constructed, excluding the cases who had a history of revascularization for PAD, the cases with ABI ≥ 1.40, and the cases with data missing.

2.2. Statistical analyses

The impact of risk factors on ABI and TBI was assessed using the linear mixed model. The bilateral measurements of ABI and TBI in each patient were used for the analysis. The analysis was on the basis of the assumption that there would be no difference between bilateral limbs in the assessment of systemic risk factors on the ABI and TBI measurements. The linear mixed model was developed as follows. The standardized values of ABI and TBI were treated as the dependent variable in a common model, in which the indication of the outcome (i.e., either standardized ABI or TBI) and a risk factor of interest were included as the fixed effects. Furthermore, to assess the difference in the impact of the risk factor between the two outcomes, an interaction term between the indication of the outcome and the risk factor was additionally entered as the fixed effect in the model. The impact of the risk factor was considered significantly different between the outcomes, if the null hypothesis that the regression estimate of the interaction term equaled to zero was statistically denied. The unadjusted regression estimate of the risk factor to each outcome was obtained in this "univariate" model.

The adjusted regression estimate of each risk factor was subsequently calculated in the "multivariate" model, in which all the risk factors of interest were simultaneously entered. The risk factors included in the model were as follows: age, sex, diabetic duration, smoking status, body mass index, eGFR, proteinuria, hypertension, dyslipidemia, stroke, and coronary artery disease. The risk factors which had a significant interaction effect in the preceding univariate model were again accompanied by their interaction term with the indication of the outcome in this multivariate model. On the other hand, the risk factors without any significant interaction effect in the preceding univariate model were considered to have a similar impact on ABI and TBI. They were therefore treated without their interaction term in the multivariate model, to obtain their common adjusted regression estimates to the outcomes.

Since the dependent variables of the current models were already standardized (i.e., the standardized values of ABI and TBI), the standardized regression estimate of a fixed effect was calculated by dividing the regression estimate by the standard deviation (SD) of the fixed effect. Consequently, the standardized regression estimate of a fixed effect β represents the increment of the standardized outcomes per one-SD increase of the fixed effect.

Data are given as mean $\pm$ SD for continuous variables and as percentages for dichotomous variables if not otherwise mentioned. Hemoglobin A1c levels were converted to a National Glycohemoglobin Standardization Program equivalent value with the conversion equation reported by the Japan Diabetes Society [10]. A p value less than 0.05 was considered to be significant and 95% confidence intervals (CI) were given when required. All statistical analyses were performed using R software Program (R Development Core Team).

3. Results

The clinical characteristics of the study population are shown in Table 1. Mean age was 63 ± 12 years and 41% were female. Diabetic duration and hemoglobin A1c levels were 15 ± 11 years and 7.4 ± 1.2%, respectively.

In the univariate analysis, age, diabetic duration, hemoglobin A1c, body mass index, eGFR and hypertension showed a significantly different impact on TBI compared to ABI (all $p < 0.05$), whereas the others did not (Table 2). The subsequent multivariate model revealed that a significant difference was still observed in the impact of age, diabetic duration, and body mass index on the outcomes (Table 3). A longer diabetic duration was associated with the decrease of both ABI ($\beta = -0.087$ [95% CI: -0.145 to -0.029]) and TBI ($\beta = -0.144$ [95% CI: -0.203 to -0.086]), but its impact was significantly greater on the decrease of TBI compared to ABI, with the difference of β -0.057 [95% CI: -0.106 to -0.009]. On the other hand, an older age and a lower body mass index were independently associated only with a lower TBI, and not with a lower ABI (Table 3). Sex, smoking, proteinuria, hypertension, and history of stroke and coronary artery disease were common independent risk factors of decreased levels of TBI and ABI (Table 3). These associations were similarly observed even after further adjustment for hemoglobin A1c levels (Table 4).

On the other hand, hemoglobin A1cl levels were not significantly associated with ABI or TBI. Even when diabetic duration was excluded from the multivariate model, the adjusted β of hemoglobin A1c levels were -0.019 [95% CI: -0.076 to 0.039] for ABI and -0.001 [95% CI: -0.059 to 0.056] for TBI, with the difference of 0.018 [95% CI: -0.030 to 0.065].

The current findings that an old age, a long diabetic duration, and a low body mass index were associated with an excess decrease of TBI compared to ABI indicate that patients with these risk factors are likely to have low TBI even if their ABI are not so decreased. To confirm this hypothesis, we supplementarily investigated the association with these risk factors and the prevalence of decreased TBI in the patients with normal ABI (>0.9). Consequently, as shown in Fig. 1, patients with more risk factors had a higher prevalence of decreased TBI.

Table 1
Characteristics of study population.

n	869
Age	63 ± 12
Female	352 (41%)
Diabetic duration (years)	15 ± 11
Hemoglobin A1c (%)	7.4 ± 1.2
Smoking	128 (15%)
Body mass index (kg/m^2)	23.8 ± 3.9
eGFR (ml/min/1.73 m^2)	69 ± 23
Proteinuria	113 (13%)
Hypertension	484 (56%)
Dyslipidemia	468 (54%)
Stroke	56 (6%)
Coronary artery disease	101 (12%)
ABI	1.12 ± 0.11
TBI	0.74 ± 0.14

Data are mean $\pm$ SD or *n* (%).