Relationship between Peripheral Arterial Disease and Incident Disability among Elderly Japanese: the Tsurugaya Project

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Aim: The aim of this study was to investigate whether peripheral arterial disease (PAD) is predictive of disability and whether the relationship between PAD and disability can be fully explained by baseline physical functions.

Methods: We followed for five years 783 Japanese aged 70 years or older without a disability at baseline in 2003. We defined participants certificated as requiring long-term care as having incident disability. The hazard ratio (HR) and 95% confidence interval (95% CI) for incident disability were calculated using the Cox proportional hazards model.

Results: After adjusting for possible confounders other than physical function, the HR of incident disability among participants with PAD was 1.86 (95%CI: 1.06 to 3.26).

Although the risk was attenuated (HR=1.63, 95%CI: 0.92 to 2.86) after adding baseline physical function as a covariate, the HR was still high. Furthermore, the relation was not statistically significant, but the group with higher physical function and PAD also had a higher HR of incident disability than those who had higher physical function without PAD.

Conclusion: PAD is an important predictor of disability even if the level of baseline physical function is high.


Key words; peripheral arterial disease, incident disability, Japanese elderly prospective cohort study, long term care insurance certification

Introduction

The Aging of society is an important public con-cern in most countries1). The number of older people with disabilities will increase as the proportion of elderly in the population increases2). Therefore, it is important to establish ways of preventing as well as delaying the onset of disabilities.

To prevent incident disability, it is important to identify those at high risk. Peripheral arterial disease (PAD) is a risk factor for stroke and dementia3-5), both of which in turn are important risk factors for disability6). Furthermore, individuals with PAD are known to have reduced physical function7-9). Thus, PAD might
be an important predictor of incident disability. However, only a few studies have investigated the relationship between PAD and disability. Furthermore, only one study has investigated the relationship between PAD and future mobility loss with reference to baseline physical function. Therefore, there is little evidence to suggest whether PAD can be used to predict disability or whether the relationship between PAD and disability can be fully explained by baseline physical function. The present study was conducted with the aim of clarifying these issues.

Methods

Study participants
The Tsurugaya project was a comprehensive geriatric assessment, which included medical status, physical function and cognitive function, performed in 2002 and 2003. In this study, we used the data for 2003 because baseline disability status as assessed by long-term care insurance (LTCI) certification was available.

Among 2925 individuals aged 70 years and older living in the Tsurugaya area of Sendai, containing the largest cities in the Tohoku area of Northern Japan, 924 gave informed consent both to participate in the study and for the follow-up of their LTCI status. Among the 924 participants, we excluded those whose ankle brachial index (ABI) had not been measured (n = 1), who had already been certificated as having a disability as assessed by the LTCI certification at baseline (n = 82), and who had not undergone a measurement of physical function (n = 58). As a result of these exclusions, we followed 783 participants in this study.

The study protocol was approved by the Ethics Committee of Tohoku University Graduate School of Medicine.

Measurements

ABI Measurement
Bilateral ABI was measured in all participants using a FORM ABI/PWV device (Colin Co., Komaki, Japan), which incorporates an automatic oscillometer. The FORM ABI/PWV has four cuffs that can measure blood pressure (BP) levels simultaneously in both arms and both legs, and automatically calculates the ABI.

This device is useful for mass medical examinations and population-based studies because it enables measurements of ABI and brachial ankle pulse wave velocity in a short time and is not affected by operator technique. Validation of this device has been reported. This device was also used in several epidemiological studies.

We defined participants with an ABI of \( \leq 0.90 \) at either leg as having PAD.

Physical function parameters
Physical function was measured using four tests: knee strength extensions, functional reach, the “Ten-meter maximum walk test” and the “timed up and go” test.

These functional tests were performed by a well trained physical therapist as described below.

Knee strength extensions
The participants were placed well back on a seat, and the waist was fixed with a belt. The knee joint was angled at 90°. Isometric contractions lasting 5 s each were conducted separated by 15-s rest intervals. Peak power was detected, calculated, and recorded in watts by a microcomputer. The average of the two highest measurements among 5 trials was recorded as isometric strength performance. To measure this function, we used an Aneropress 3500 (Combi Wellness, Tokyo).

To minimize differences in body mass, leg extension power was expressed as the average peak of the leg relative to body weight (W/kg).

Functional reach
We also measured how far an individual can reach forward beyond arm’s length while maintaining a fixed base of support in a standing position, without losing balance. We attempted the test twice and adopted the higher of the two scores.

Ten-meter maximum walk test
Each participant was asked to walk 10 m at maximum speed. A stopwatch was used for timing, and a counter was used to obtain the number of steps. To eliminate periods of acceleration and deceleration, the participants started walking 3 m before entering the walkway and stopped walking 3 m beyond its end. The test was repeated three times, and the data for the fastest walk were recorded.

“Timed up and go” test
The participants were seated in a free-standing padded armchair (46 cm high) and asked to rise (with or without using the arm rests), walk to a mark 3 m away, turn around, and walk back to the chair and sit down. The time between rising from the seat and
making contact with the back of the seat was measured in seconds. This test was repeated three times and the time of the fastest trial was recorded\(^{12}\).

**Other measurements**

Information on smoking status, history of diseases and physical activity was obtained using questionnaire. Drug information was confirmed by an experienced pharmacist\(^{12}\).

Casual BP was measured using an automated device (HEM747IC: Omron Life Science Co., Ltd., Tokyo, Japan)\(^{10}\). BP was measured at screening under resting conditions. Participants were considered to be hypertensive if their systolic BP was at least 140 mmHg or diastolic BP was at least 90 mmHg, or if they were taking antihypertensive agents. Participants were considered to have a high blood glucose concentration if their casual (non-fasting) blood glucose level was at least 7.77 mmol/L, or if they used antidiabetic medication\(^{10, 23}\). With regard to physical activity, we obtained information on the frequency and duration of walking, brisk walking and sports by self-reported questionnaire. Based on this information, we defined 6 levels of physical activity as described in our previous report\(^{15}\). Physical activity was assessed as leisure time physical activity. We classified into three subcategories according to the frequency and duration of walks or workouts as follows.1) High, 3 of more times per week for at least 30 min each time. 2) Low, some activity in the past year, but not enough to meet the criteria for the high group; and 3) None, no LTPA. Finally, we used these categories and subcategories to define the following six levels of LTPA 1) Level 1, no sports, no brisk walking, no walking; 2) Level 2, no sports, no brisk walking, low amount of walking; 3) Level 3, no sports, no brisk walking, high amount of walking; 4) Level 4, no sports, low amount of brisk walking, any amount of walking; 5) Level 5, no sports, high amount of brisk walking, any amount of walking; 6) Level 6, any amount of sports, any amount of brisk walking, any amount of walking. We defined higher physical activity levels as at least brisk walking (Level 4-6) in this study.

**Outcome measurement**

**Long-term care insurance certification**

Incident disability was assessed by LTCI certification. The LTCI system was launched as part of the national insurance system in April 2000\(^{22-24}\). We followed up incident disability for five years.

In Japan, people aged 40-64 years who are diagnosed with aging-related diseases (e.g. Alzheimer’s disease and stroke) and those aged ≥65 years who are certified as requiring care are eligible for benefits based on level of care under the LTCI system\(^{15}\). To receive LTCI services, an elderly person or his/her caregiver (family or professional) must contact the municipal government to have the applicant’s care needs officially certified\(^{23}\). A trained local government official visits the applicant’s home to evaluate nursing care needs using a questionnaire assessing current physical and mental status and use of medical procedures\(^{23}\). These results are entered into a computer to calculate the applicant’s standardized scores for physical and mental functions, estimate the amount of time required for care for the nine categories (grooming/bathing, eating, using the toilet, transferring, eating, assistance with instrumental activities of daily living, behavioral problems, rehabilitation, and medical services)\(^{23}\). Based on the nationally determined system, it is decided whether the applicant deserves to be certified as eligible for LTCI services and the system assigns a care-needs level determined by a confirmed certification board consisting of physicians, nurses and other experts in health and social services appointed by the local mayor.

The care-needs level consists of 7 levels which are well correlated with the Barthel Index (Spearman’s coefficient: −0.86) and the Mini-Mental State Examination (Spearman’s coefficient: −0.42)\(^{24}\). The definition is considered a comprehensive measure of disability in the elderly\(^{25}\). We asked the Sendai city municipal authority to provide information on LTCI certification including care level and date of certification, annually up until June 30\(^{th}\), 2008 (for 5 years).

**Statistical analysis**

Baseline characteristics were compared by the \(\chi^2\) test and \(t\)-test, as appropriate (Table 1). The hazard ratio (HR) and 95% confidence interval (95%CI) for the relationship between PAD and incident disability was calculated using a Cox proportional hazards model (Table 2). We censored participants who died or moved away during follow-up. We also analyzed the relationship between PAD and composite outcome of disability or mortality.

For the Cox proportional hazards modeling, we used an age-sex adjusted model (Model 1); a multiple adjustment model adjusted for smoking status, hypertension, high blood glucose level, history of stroke and physical activity (Model 2); and a third model to confirm the effect of lower physical function in PAD participants on the relationship between PAD and disability, with baseline values of all physical functional
To adjust for physical function, we assigned each function a score of 1 to 4 according to the sex-specific physical function quartile and added these scores as covariates (continuous). To assess whether PAD is predictive of disability independent of physical function, we conducted a combination analysis. To create a combined category, we used the median value of physical function as the cut-off. As a result, four combined categories were established, i.e. high physical function without PAD, high physical function with PAD, low physical function without PAD and low physical function with PAD. In these analyses, we used the group with high physical function without PAD as a reference.

The level of statistical significance was set at \( p < 0.05 \). All statistical analyses were performed with SAS software, version 9.1 (SAS Institute, Cary, USA).

## Results

Table 1 shows baseline characteristics according to the presence or absence of PAD.

Mean age was significantly higher in participants with PAD than those without PAD.

The proportions of men, current and past smokers, and subjects with hypertension, high blood glucose levels and stroke also were significantly higher among the participants with PAD than those without PAD.
PAD. Physical functions were consistently worse in participants with PAD, the difference being statistically significant for the timed up and go test and ten-meter maximum walk test. Table 2 shows the relationship between PAD and incident disability. During the five years of follow-up, among 783 participants, 33 died, and 7 transferred. We observed 155 incident disability cases during the follow-up period. Compared with participants without PAD, the age-sex adjusted HR for incident disability was 2.12 (95%CI: 1.22 to 3.69) in participants with PAD, model 1. After adjustments for further possible confounding factors, the HR for incident disability among participants with PAD was 1.86 (95%CI: 1.06 to 3.26) in model 2. Because physical function might be a symptom of PAD, we considered Model 2 to be the most important for estimating the relation between PAD and incident disability. After additional adjustments for physical functions, the HR for incident disability among participants with PAD was 1.63 (95%CI: 0.92 to 2.86) in model 3.

When we used composite outcome of disability or mortality, the results in Models 1, 2 and 3 were 2.18 (95%CI: 1.33 to 3.56), 1.84 (95%CI: 1.12 to 3.04), and 1.67 (95%CI: 1.01 to 2.76), respectively.

Table 2 shows the HR for incident disability using a combination of PAD status and physical function status. For every baseline physical function, the HR for incident disability was highest among PAD patients with low physical function, and the increase in risk was statistically significant. Although not statistically significant, the HR for disability tended to be higher among participants with high physical function with PAD than participants with high physical function without PAD, except for functional reach.

**Discussion**

The present study demonstrated that the participants with PAD had an increased risk of disability compared with the participants without PAD. Because adjustments for baseline physical function attenuated this relationship, the poorer physical function in PAD patients played an important role in incident disability. However, the risk was still high even after the adjustments for baseline physical function, and PAD patients with higher physical function also had a higher risk of incident disability. Thus, the relationship between PAD and disability was not fully explained by baseline physical function.

Our study had several strengths. First, it measured both ABI and several physical functions such as muscle strength, balance and velocity of walking. Thus, we were able to assess whether PAD is predictive of disability independent of these physical functions. This paper is the second to have investigated the association of PAD with disabilities including an adjustment for baseline physical function. Second, we
used an objective measure of disability. The LTCI certification is determined on the basis of strictly established uniform rules throughout Japan\textsuperscript{24, 25}. The certification correlates with not only physical function but also cognitive function\textsuperscript{24, 25}.

Only two prospective studies have evaluated the relationship of PAD with loss of mobility. Mc Dermott et al. reported that during 24 months of follow-up, the subjects with PAD had a higher rate of mobility loss than those without PAD\textsuperscript{8}. They defined mobility loss as being unable to walk a quarter mile or walk up and down one flight of stairs without assistance. However, in their first paper, they did not adjust for baseline physical function\textsuperscript{8}. They also analyzed the association between PAD and mobility loss after 50 months of follow-up including adjustments for baseline physical function\textsuperscript{9}. Their study indicated that the participants with PAD had greater mobility loss than those without PAD before adjustments for baseline physical function (HR = 1.63, \textit{p}-value: 0.036), and that this association was attenuated significantly after the adjustments for baseline physical function (HR = 1.00-1.53, \textit{p}-value: \geq 0.094)\textsuperscript{9}. From these results, they concluded that the association between PAD and mobility loss was explained by poor baseline functional performance\textsuperscript{9}.

In the present study, we investigated whether PAD was associated with incident disability independent of baseline physical function. After adjustments for baseline physical function, the risk was substantially attenuated. We considered that our findings were consistent with those of Mc Dermott \textit{et al.} in terms of baseline physical function playing an important role in the relationship between PAD and disability. However, in our study, the HR of incident disability was still higher in the participants with PAD than in those without PAD. Additionally, the association of PAD with disability or mortality was statistically significant when we used a composite outcome of death and disability. Furthermore, compared with the group that showed high physical function without PAD, the group with higher physical function with PAD also had a higher HR of incident disability. The discrepancy between our study and that of Mc Dermott \textit{et al.} might have been due to the difference in the endpoint, i.e., they used mobility loss and we used a comprehensive endpoint, LTCI certification. Because patients with PAD are reported to have a higher risk of incident stroke or dementia, especially, vascular dementia, not only physical function but also these pathways might contribute to the increase in risk\textsuperscript{3, 6}. However, because we did not clarify the reason for incident disability, we were unable to confirm whether the risk increase was explainable by stroke or dementia.

Our study also had some limitations. First, we used the date of LTCI-certification as the date of incident disability. Thus, the date of incident disability would be later than the true date. However, as with other diseases, it is hard to correctly estimate the date of incident disability. Therefore, we considered our approach using objective information on incident disability assessed by LTCI certification to be acceptable. The prevalence of PAD is lower in Japan than in Europe or the United States\textsuperscript{18, 26}. Furthermore, we excluded participants already been certificated as having a disability at the baseline. Therefore, the prevalence of PAD in this study was small (about 4.5\%). This low prevalence limited the statistical power of the study. Larger prospective studies in Japan will be required to corroborate our findings.

In conclusion, we have found that PAD is predictive of incident disability. The high risk of incident disability in PAD participants cannot be fully explained by baseline physical function. Therefore, we conducted that PAD is an important predictor of disability even if the level of baseline physical function is high.

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