Progression of Lower-Extremity Disability in Older Women With Diabetes

The Women's Health and Aging Study

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OBJECTIVE — Older patients with diabetes are more likely to have a higher prevalence of multiple risk factors for physical disability, as a result of diabetic complications. We evaluated the pace of decline in lower-extremity function and the risk for progression of disability in older women with diabetes.

RESEARCH DESIGN AND METHODS — We conducted a 3-year longitudinal cohort study of a random sample of 729 physically impaired older women (age ≥65 years) living in the community (Baltimore, MD). Diabetes was ascertained by standard criteria. Self-reported functional status and objective performance measures were assessed at baseline and over six semi-annual follow-up visits.

RESULTS — The baseline prevalence of diabetes was 14.4%. After adjustment for age and compared with women without diabetes, those with diabetes had an RR of 1.8 (95% CI 1.3–2.5) for incident mobility disability and 1.6 (1.2–2.1) for incident activity of daily living disability. The increased incidence of new disability associated with diabetes was paralleled by a greater decline in objective measures of lower-extremity function. Adjustment for multiple risk factors for disability did not significantly attenuate the risk for disability associated with diabetes.

CONCLUSIONS — In older patients, impaired lower-extremity function is a long-term diabetic complication. Comprehensive assessment of older diabetic patients should include a standardized evaluation of lower-extremity performance.

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D iabetes has been consistently reported as one of the strongest correlates of the presence of poor lower-extremity performance or mobility difficulty (1–3), and older patients with diabetes are at high risk for loss of independence (4). This is not surprising because a number of factors involved in the disablement process in older people, including cardiovascular diseases, peripheral neuropathy, overweight, osteoarthritis, visual deficit, and cognitive impairment, are more prevalent in diabetic patients (5).

Despite a large amount of cross-sectional information, scant data are available on the effect of diabetes on decline over time in lower-extremity function and on progression of disability in very old patients. In other words, it is not known whether diabetes still has a negative effect on physical function in older people, independent of the accumulated effect of multiple diabetes-related medical conditions affecting lower-extremity performance. Diabetes is highly prevalent in older people, and its prevalence is expected to rise steeply in the next decades (6).

The Women's Health and Aging Study (WHAS) (7) is a longitudinal study designed to identify factors associated with progression of physical disability in physically impaired older women living in the community. We hypothesized that compared with women without diabetes, diabetic women would have an increased likelihood of functional decline and progression of disability. The main aim of the study was to evaluate the extent to which the excess risk for disability associated with diabetes was attributable to a greater prevalence of comorbidities and impairments that are common complications of diabetes.

RESEARCH DESIGN AND METHODS

Sample
The WHAS is an epidemiological study of the causes and course of disability among the one-third most-disabled women aged ≥65 years living in the community (7). Briefly, among 5,316 community-dwelling women randomly sampled from Medicare beneficiaries in Baltimore, Maryland, 1,409 were eligible for the study because of a Mini Mental State Examination (8) score ≥18 and difficulty in performing one or more tasks in at least two of the following four domains of functioning: mobility/exercise tolerance, upper-extremity abilities, basic self-care, and higher-functioning tasks of independent living. Overall, 1,002 women (71% of those eligible) agreed to participate in

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the study. Participants were reevaluated over six semiannual follow-up visits. The Johns Hopkins University institutional review board approved the study, and all participants gave informed consent.

Because we were interested in evaluating the association between diabetes and risk of decline in lower-extremity function, for this specific analysis we excluded participants who, at baseline, were unable to walk (*n* = 73) or had severe walking limitation (walking speed <0.4 m/s, *n* = 200) (9).

Measures of physical function
Self-reported information included difficulty with two mobility-related tasks (walking one-quarter of a mile and climbing stairs) and four basic activities of daily living (ADLs; bathing, transferring from bed to chair, using the toilet, and dressing). Responses were coded as: none, a little, some, a lot, or unable to perform the task. Using this information, two different outcomes were defined: mobility disability (a lot of difficulty or inability to walk one-quarter of a mile and/or to climb stairs), ADL disability (a lot of difficulty or inability in at least one ADL). Objective measures of lower-extremity function included three timed tests: usual 4-m walking speed, a five chair stands test, and a hierarchical test of balance. These tests were administered following a standardized protocol (7). The results of the three performance tests were used to construct a summary performance score of lower-extremity function. The score, measured by a 0–12 ordinal scale, represents the sum of the scores of the three individual tests (from 0 to 4) (10). For women with missing data during the follow-up, if two or three of the individual test scores were missing, the total score was set to missing; otherwise, if only one test score was missing, the summary score was calculated as follows: (sum of the nonmissing scores) × 1.5 (11).

Diabetes and comorbidities
Diabetes was ascertained at baseline using a specific standardized algorithm (7). The algorithm utilized data from multiple sources of information as previously described (2). Disease-specific algorithms were also used to assess the prevalence of coronary heart disease, congestive heart failure, stroke, and hypertension. Peripheral arterial disease was assessed by the

ankle-brachial index, measured using a Doppler stethoscope (Parks model 841-A). An ankle-brachial index value <0.9 was considered diagnostic (12). Five subjects with values ≥1.5 were considered as missing (13). Large-fiber sensory nerve function was quantified by measuring the vibration perception threshold with a Vibratron II (Physitemp Instruments, Clifton, NJ). Participants were categorized in three groups according to detection of small vibratory stimuli, as follows: *1*) normal function (<3.43 vibration units), *2*) mild to moderate dysfunction (3.43 to <6.31 units), and *3*) severe dysfunction (≥6.31 vibration units) (14). Visual impairment was defined as visual acuity ≤20/40 (with corrective lenses, if used) (15).

Potential confounders
BMI (kg/m^2) was computed using measured height and weight. Values between 25 and 29.9 were considered overweight, and values >30 were considered obese (16). Depressive symptoms were assessed by the 30-item version of the Geriatric Depression Scale (cut point ≥14) (17), and presence of cognitive impairment was defined as a Mini Mental State Examination score <24 (8). Presence of knee osteoarthritis and hip fracture was also considered. Information on years of education and smoking status (never, former, or current) was collected from the baseline interview. Participation in any regular exercise program and walking for exercise (time/week) was determined from the baseline interview and was used as an overall indicator of physical activity level.

Statistical analysis
Age-adjusted Kaplan-Meier curves were fitted to explore the effect of diabetes on time to onset of new mobility and ADL disability. Cox proportional-hazard models were then used to estimate the adjusted RRs of mobility and ADL disability according to diabetes status. Those surviving with no new disability were censored at the date of the last follow-up, those dying with no new disability were censored at the time of their deaths. Subjects who at baseline were already disabled were excluded from the analysis. Covariates hypothesized to be potential confounders or potential mediators of the association between diabetes and physical function were progressively added to the

models. The Cox model assumes that the hazard ratio of participants with and those without diabetes remains constant over time. We found a significant interaction between the presence of diabetes and time to onset of new ADL disability (*P* = 0.04). Because of this interaction, we ran separate models for two different follow-up periods (0–18 and 19–36 months) to compute the RR for ADL disability. We examined the effect of diabetes status on change over time in objective measures of lower-extremity function, using random-effects models (18).

RESULTS — Of 729 WHAS participants included in this analysis, 105 (14.4%) had an adjudicated diagnosis of diabetes at baseline. The mean age of the study population was 77.4 years. Compared with participants without diabetes, those with diabetes were younger, more likely to be black, and less likely to be current smokers (Table 1). Women with diabetes had poorer summary performance scores and were more likely to have mobility or ADL disability. Additionally, these women were more likely to have cardiovascular conditions, peripheral nerve dysfunction, visual impairment, and elevated BMI.

Figure 1 shows the Kaplan-Meier survival curves exploring the association between diabetes and time to disability onset. The risk of new mobility disability (Fig. 1*A*) and ADL disability (Fig. 1*B*) was significantly higher for women with diabetes. However, the risk of ADL disability associated with diabetes was clearly higher in the late part of the follow-up (19–36 months), whereas no difference emerged during the first 18 months. In proportional hazard models, adjusted for age, race, and smoking, women with diabetes had an RR of 1.78 (95% CI 1.25–2.53) for new mobility disability and an RR of 1.57 (1.15–2.14) for new ADL disability (Table 2). The analysis stratified by follow-up period showed that in the late part of the follow-up (19–36 months), women with diabetes had a 2.4-fold risk (2.38 [1.52–3.17]) of ADL disability compared with women without diabetes. The risk estimates for mobility and ADL disability were only moderately reduced after additional adjustment for potential confounders, including objective measures of baseline functional status, and for the conditions for which diabetes is an

Table 1—*Baseline general and health-related characteristics by diabetes status*

Characteristics	Without diabetes (n = 624)	With diabetes (n = 105)	P*
Age (years)	77.9 ± 0.3	74.6 ± 0.6	<0.01
African-American	23.4	37.1	0.02
Education ≥12 years	38.9	32.3	0.20
Smoking status			
Former	31.9	42.6	0.22
Current	18.0	9.5	<0.03
Use of oral hypoglycemic agents	—	52.4	—
Use of insulin	—	30.5	—
Years since first clinical diagnosis of diabetes	—	10 (<1–41)	—
Functional status			
Mobility disability	46.0	52.4	0.18
ADL disability	21.3	25.7	0.22
Summary performance score (0–12)	7.3 ± 0.1	7.0 ± 4	<0.01
Physical activity (hours/week)			
>0–3	31.9	36.2	0.58
>3	10.3	8.6	0.52
Conditions for which diabetes is a risk factor			
Directly affecting lower extremity function			
Ankle-brachial index <0.9	24.6	43.0	<0.01
Peripheral nerve dysfunction			
Mild to moderate	34.4	44.3	<0.01
Severe	16.1	14.4	0.24
General			
Coronary heart disease	29.8	40.0	<0.05
Congestive heart failure	7.1	14.3	<0.02
Stroke	4.2	5.7	0.53
Hypertension	58.9	77.1	<0.01
Visual impairment	19.4	23.2	<0.03
Potential confounders			
Overweight (BMI 25–29.9 kg/m²)	35.0	35.2	<0.05
Obesity (BMI ≥30 kg/m²)	32.5	48.6	<0.01
Knee osteoarthritis	42.2	49.5	0.32
Hip fracture	3.9	3.8	0.54
Cognitive impairment (MMSE <24)	12.5	16.2	0.06
Severe depression symptoms (GDS ≥14)	13.0	18.1	0.23

Data are means ± SE, %, or median (range). *Age-adjusted *P* values comparing women with diabetes to women without diabetes. MMSE, Mini Mental State Examination.

established risk factor (RR for mobility disability 1.63 [1.12–2.36]; RR for ADL disability, late follow-up period, 2.18 [1.33–3.60]). To evaluate the importance of duration of diabetes, we stratified the analysis by duration of the disease (no diabetes, diabetes for ≤10 years, and diabetes for >10 years). The fully adjusted risk for mobility disability was very similar in the two groups of diabetic women: 1.62 (1.01–2.59) for women with ≤10 years of disease and 1.64 (0.96–2.78) for the other group. For ADL disability (late follow-up period) the risk tended to be greater for women with longer duration of disease (2.66 [1.37–5.15]) but was substantial also for women with ≤10 years of diabetes duration (1.86 [1.00–3.45]).

The relationship between diabetes and decline in objective measure of lower-extremity function was investigated estimating the change in summary performance score over 3 years according to diabetes status (Table 3). Overall, both groups of women experienced a significant decline in lower-extremity function score over time (all *P* values <0.001). However, differences between the two groups became more pronounced as time progressed. In the fully adjusted random-effect model, women with diabetes had an estimated average decline per year 38% greater than those of women without diabetes (0.91 vs. 0.66 points/year), and the difference between the slopes was statistically significant.

Data on glycosylated hemoglobin were available in 510 participants. In this subgroup, the adjusted RR associated with diabetes was 2.0 (95% CI 1.33–3.09) for mobility disability and 2.38 (1.34–4.22) for ADL disability. After further adjustment for glycosylated hemoglobin, the excess risk associated with diabetes was reduced by 36% for mobility disability (1.64 [0.95–2.83]) and by 65% for ADL disability (1.48 [0.69–3.15]), and the risks were no longer statistically significant.

CONCLUSIONS — This study demonstrated that older women with diabetes are at greater risk for decline in lower-extremity function and for development of severe disability than nondiabetic women over a 3-year period. The results were consistent using complementary analytical approaches and both self-reported and objective measures of physical function. Although established risk factors for disability were more common among patients with diabetes, in multivariate analyses, adjusted for prevalent chronic conditions and impairments, the association between diabetes and progression of disability remained relevant and statistically significant. This suggests that the negative effect of diabetes on physical function over time was in addition to the presence of traditional diabetes complications at baseline.

Our findings extend the results of previous longitudinal studies. Seeman et al. (19) demonstrated that in high-functioning older people, diabetes is one of the strongest predictors of decline in physical performance. Additionally, a recent report from the Study of Osteoporotic Fractures (SOF) demonstrated that among nondisabled older women, subjects with diabetes had a twofold risk of incident disability compared with women without diabetes (20). To the best of our knowledge, however, our study is the first to demonstrate that in older and already physically impaired women, diabetes is still an independent risk factor for steeper decline in lower-extremity function and
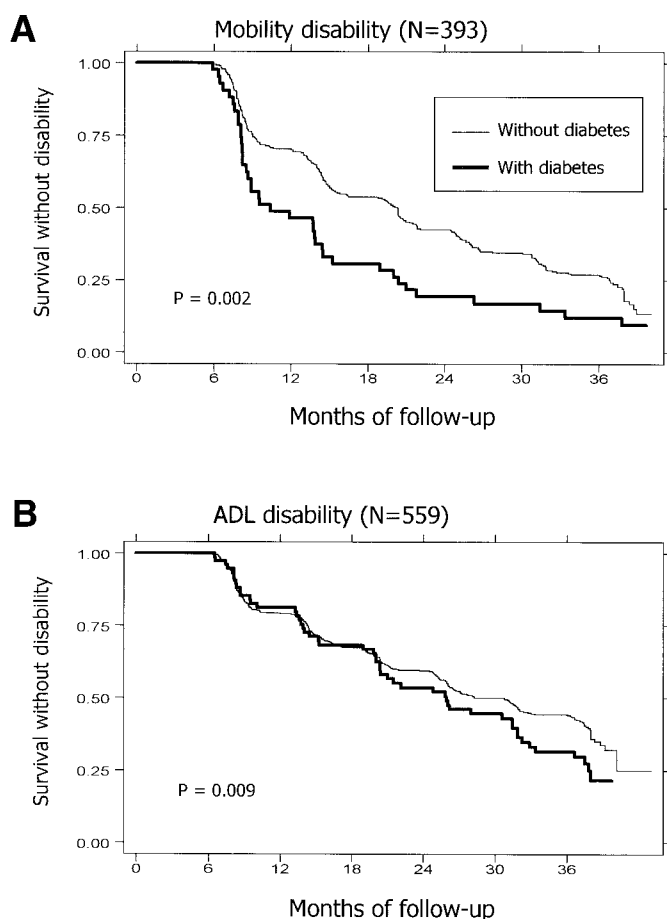
A

Mobility disability (N=393)

B

ADL disability (N=559)

Figure 1—*Age-adjusted Kaplan-Meier survival curves exploring the association between diabetes and risk of developing mobility disability (A) and ADL disability (B). The number of women who were considered initially at risk is reported on top of each panel.*

explain why diabetes is associated with decline in lower-extremity function independent of the baseline level of clinical complications. First of all, compared with subjects without diabetes, older patients with diabetes may be at higher risk for new onset or progression of a wide range of microvascular and macrovascular complications (21,22). It has been suggested that in older patients, the mechanism linking diabetes and the disablement process is multifactorial (1,2). Therefore, it may be hypothesized that even a small progression in multiple complications may play an important role in accelerating the decline in physical function over a relatively short period of time. From this point of view, it is interesting to note that in our analysis, the relationship between diabetes and risk of disability was partially explained by the level of glycemic control, a powerful predictor of the development and progression of diabetic complications. Unfortunately, we lacked objective information on change over time in visual acuity, peripheral neuropathy, peripheral arterial disease, and other diabetic complications, which would have allowed us to formally test this hypothesis.

A second potential explanation is that other diabetes-related mechanisms, different from the traditional diabetic complications, may be involved. It is well known that age-related loss of muscle mass, a phenomenon referred to as sarcopenia, is a powerful risk factor for disability (23). In older people, the presence of diabetes may accelerate the loss of muscle. For example, diabetes has been associated with increased circulating levels of proinflammatory cytokines (24), which, in turn, have been

for progression to severe disability and loss of independence. Moreover, our results suggest that the higher risk for developing severe disability associated with diabetes is not explained by a greater burden of preexisting complications. Therefore, other components of the causal

pathway leading from diabetes to disability should be hypothesized and investigated. Understanding the nature of these components may offer new opportunities for treatment of the disabling effect of diabetes.

Several biological mechanisms may

Table 2—*Multivariate relative risks relating diabetes to new onset of mobility disability and ADL disability*

Disability	Events per person at risk		RR (95% CI)		
	Without diabetes	With diabetes	Model 1	Model 2	Model 3
Mobility disability*	244/344	39/49	1.78 (1.25–2.53)†	1.76 (1.24–2.05)†	1.63 (1.12–2.36)†
ADL disability‡					
All	268/484	51/75	1.57 (1.15–2.14)†	1.39 (1.01–1.91)§	1.39 (0.99–1.94)
1–18 months	147/484	23/75	1.12 (0.71–1.77)	0.95 (0.60–1.52)	0.91 (0.56–1.48)
19–36 months	121/305	28/46	2.38 (1.52–3.71)‖	2.21 (1.40–3.49)†	2.18 (1.33–3.60)†

Model 1: adjusted for age, race, and smoking. Model 2: adjusted for factors in model 1 plus BMI, knee osteoarthritis, cognitive impairment, depressive symptoms, and baseline summary performance score. Model 3: adjusted for factors in model 2 plus diagnosis of hypertension, stroke, coronary heart disease, congestive heart failure, ankle-brachial index <0.9, peripheral nerve dysfunction, and visual impairment. *A total of 336 women were excluded from the analysis because of severe mobility disability at baseline; †$P < 0.01$; ‡170 women excluded from the analysis because of severe ADL disability at baseline; §$P < 0.05$, ‖$P < 0.001$.

Table 3—*Change in summary performance score (0–12) over time by diabetes status, estimated from random-effect models*

	Model 1			Model 2		
	β	SE	*P*	β	SE	*P*
Disease status						
Without diabetes						
Intercept	7.50	0.1	—	8.61	0.35	—
Change per year	−0.66†	0.045	—	−0.66†	0.045	—
With diabetes						
Intercept	6.83	0.25	0.013*	8.44	0.44	0.546*
Change per year	−0.96†	0.11	0.014‡	−0.91†	0.12	0.014‡

Model 1: adjusted for age. Model 2: adjusted for age, race, smoking, BMI, knee osteoarthritis, cognitive impairment, depression, hypertension, stroke, coronary heart disease, congestive heart failure, ankle-brachial index <0.9, peripheral nerve dysfunction, and visual impairment. *P values are for null hypothesis of same intercept; †$P < 0.001$ for the hypothesis of β coefficient (slope) = 0; ‡P value for the interaction term between time and diabetes testing the hypothesis that the average rate of decline in the dependent variable is statistically different between women with and without diabetes.

proposed as a risk factor for sarcopenia and incident disability in older people (25). Although we did not collect direct indicators of muscle mass change over time, our data indirectly support this hypothesis. Indeed, women with diabetes had a greater decline in lower-extremity summary performance score, a measure highly correlated with muscle strength and, in turn, with muscle mass (26). Moreover, compared with their nondiabetic counterparts, diabetic women also experienced a greater decline in the strength of their knee extensor muscles (data not shown).

Third, other diabetes complications not investigated in this study may play an important role in the disablement process of older people with diabetes. We do not have information on diabetic nephropathy and on other types of diabetic neuropathy, including proximal motor neuropathy, which may cause weakness of the proximal muscles of the legs, resulting in difficulty or inability to walk and rise from the sitting position. In addition, although we considered a wide spectrum of comorbidities, we had scant data on disease severity. It is remarkable, however, that adjustment for an objective measure of lower-extremity function at baseline only slightly attenuated the risk of new severe disability associated with diabetes. These tests of lower-extremity performance predict a number of health outcomes in older, nondisabled people and are likely to capture information on several factors, including disease presence and severity,

physiological decline, and motivation (27).

An additional limitation of this study was that the algorithm used for diabetes ascertainment did not include a fasting glucose level. Consequently, according to American Diabetes Association criteria (28), some women with fasting glucose levels ≥126 mg/dl might have been classified as nondiabetic. Newly diagnosed older diabetic patients have greater prevalence of cardiovascular disease compared with subjects without diabetes (29). Notably, even short-term glycemic control has been associated with a reduction in several symptoms, including pain, dizziness, and fatigue (30). This evidence suggests that we might have underestimated the strength of the association between diabetes and the risk of functional decline.

Older women with diabetes are at greater risk for lower-extremity disability than their nondiabetic counterparts; this finding suggests that in older people, impaired lower-extremity performance is a major long-term diabetic complication. Clinical assessment of older diabetic patients should include a standardized evaluation of lower-extremity performance to facilitate early detection of functional decline. Our results also suggest that the degree of glycemic control might play an important role in the disablement process of older people with diabetes. Future studies should investigate whether stricter glycemic control would slow the decline in physical function in older people.

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