Diabetes Is Associated With Subclinical Functional Limitation in Nondisabled Older Individuals

The Health, Aging, and Body Composition study

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OBJECTIVE — The aim of this study was to examine the role of comorbid conditions and body composition in the association between diabetes and subclinical functional limitation, an indication of early functional decline, in well-functioning older individuals.

RESEARCH DESIGN AND METHODS — This was a cross-sectional analysis of 3,075 well-functioning black and white men and women aged 70–79 years, enrolled in the Health, Aging, and Body Composition study. Diabetes was defined by self-report and/or hypoglycemic medication use or fasting glucose ≥126 mg/dl. Subclinical functional limitation was defined using self-report of capacity and objective performance measures. Comorbid conditions were identified by self-reported diagnoses, medication use, and clinical measures. Body composition measures included anthropometry and total fat (dual X-ray absorptiometry).

RESULTS — Of 2,926 participants, 1,252 (42.8%) had subclinical functional limitation at baseline. Among 2,370 individuals without diabetes, 40% had subclinical functional limitation, whereas the prevalence was 53% among the 556 diabetic participants with an age/sex/race-adjusted odds ratio (OR) 1.70 (95% CI 1.40–2.06). This association remained significant when adjusted for body composition measures (OR 1.54 [1.26–1.88]), diabetes-related comorbidities, and other potential confounders (OR 1.40 [1.14–1.73]). In the fully adjusted model, consideration of HbA_{1c} (< or ≥7%) and diabetes duration showed that poor glycemic control in diabetic individuals explained the association with subclinical functional limitation.

CONCLUSIONS — In a well-functioning older population, diabetes is associated with early indicators of functional decline, even after accounting for body composition and diabetes-related comorbidities. Poor glycemic control contributes to this relationship. Whether improvement in glycemic control in older people with diabetes would change this association should be tested.

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Abbreviations: DXA, dual X-ray absorptiometry; Health ABC, Health, Aging, and Body Composition.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Nearly one-fifth of U.S. adults over age 60 years have diabetes, and by the year 2025, some reports predict that two-thirds of the diabetic population in developed countries will be elderly (1,2). Diabetes is a strong predictor of reported disability and poorer physical performance in older U.S. adults (3–5).

However, there is controversy about whether diabetes itself increases risk of loss of independence or if the dependency results from other chronic underlying diseases (6). Diseases and impairments, including coronary heart disease, hypertension, peripheral arterial disease, stroke, peripheral neuropathy, and visual and cognitive impairment are more common in the diabetic population. This excess morbidity could explain the association of diabetes with physical disability. Few studies have focused on the specific mechanisms contributing to disability in older diabetic individuals, and it is still unclear if the disablement process is a direct consequence of diabetes or results from diabetes-related comorbidities and complications (7,8).

Physical disability and dependency in older adults are measured by self-reported function in activities of daily living and instrumental activities of daily living and/or by objective physical performance measures (9). Although commonly used to quantify function, activities of daily living and instrumental activities of daily living lack the sensitivity and discriminatory power needed to identify early decline defined as preclinical disability by Fried et al. (10). Preclinical declines in function can be identified by self-report (11) and performance measures (12), and both are predictors of incident disability (10). Understanding the mechanisms of the relationship between subclinical functional limitation and diabetes in well-functioning elderly will guide early interventions to delay onset and progression to severe limitation or disability (13,14). No study to date has

focused on early indicators of functional decline, here called subclinical functional limitation, in older diabetic individuals.

This study examined the association between diabetes and subclinical functional limitation in a well-functioning cohort. We hypothesized that this association would be explained by body composition, including higher BMI and higher body fat. We also hypothesized that subclinical functional limitation would be secondary to comorbid health conditions and complications related to diabetes or potential confounders (e.g., osteoarthritis, depression, physical activity, smoking) rather than independently related to diabetes.

RESEARCH DESIGN AND METHODS

Study population

Data are from the Health, Aging, and Body Composition (Health ABC) study, a 9-year longitudinal cohort study designed to investigate the relationships among health conditions, body composition, social and behavioral factors, and functional decline. The study population consists of 3,075 well-functioning black and white men and women aged 70–79 years, 48% men, and 42% blacks. Whites were recruited from a random sample of Medicare beneficiaries residing in designated zip code areas surrounding the Pittsburgh, Pennsylvania, and Memphis, Tennessee, field centers. Blacks were recruited from all age-eligible black community residents in these geographic areas. All potential participants received a mailing, followed by a telephone eligibility screen. The cohort was selected to be free of functional limitation defined as difficulty in walking one-quarter mile or walking up 10 steps without resting. Additional exclusions included: *1*) difficulty performing activities of daily living; *2*) use of a cane or other equipment to get around; *3*) history of active treatment for cancer in the prior 3 years; and *4*) plans to leave the area within 3 years. A detailed interview on social demographics, health behaviors, indicators of socioeconomic status, and health service use was administered in the home. Participants underwent a clinic-based examination that included standardized biological and body composition measures, indicators of weight-related health conditions, and physical performance measures. The baseline home interview and clinic-based examination were carried out between April 1997 and June 1998. All participants gave written informed consent, and all protocols were approved by the institutional review boards at both study sites.

Measures of subclinical functional limitation

Subclinical functional limitation was assessed by self-reported ease of walking and climbing stairs and by objective physical performance measures.

Self-reported subclinical functional limitation

Participants who reported difficulty performing any of the following tasks (walking 1 mile, rising up from a chair without using arms, or walking up 20 steps without resting) were defined as having subclinical functional limitation. Different levels of severity in subclinical functional limitation were also defined by adding the number of difficulties reported (maximum score of 3).

Objective physical performance measures as measure of subclinical functional limitation: summary physical performance measure

We modified a brief battery of three lower-extremity performance tests used in the Established Populations for the Epidemiologic Studies of the Elderly consisting of five repeated chair stands, standing balance (semi- and full-tandem stands), and a 6-m walk to determine usual gait speed (15). We added a narrow walk test of balance administered at the same course as the 6-m walk. The development and validation of this summary measure have been described in detail elsewhere (16). To standardize, all measures were converted to ratios scaled between 0 and 1, so the range of the summary physical performance score is from 0 to 4. Forty-four participants with missing values for the summary physical performance score were imputed with median score for the whole group.

Diabetes assessment

Participants were asked if a doctor had ever told them of a diagnosis of diabetes, excluding the occurrence of diabetes during pregnancy in women. Prescribed and over-the-counter medications used in the preceding 2 weeks were brought to the clinic by the participants. We defined diabetes as *1*) a report of having been told of diabetes, *2*) use of oral hypoglycemic medications or insulin, and/or *3*) having a fasting plasma glucose ≥126 mg/dl (17). Fasting glucose was available for 99% of the participants. We used information on reported age at diagnosis to define diabetes duration; participants considered diabetic as a result of fasting glucose only were considered to have new-onset diabetes. All participants had an HbA_{1c} test performed (Bio-Rad, Hercules, CA), and poor glycemic control was defined by HbA_{1c} ≥7%. Glucose parameters were measured on a Vitros 950 analyzer (Johnson and Johnson, Rochester, NY). Biological specimens were processed according to standardized protocols by the Laboratory of Clinical Biochemistry at the University of Vermont.

Diabetes-related comorbidities and impairments

Peripheral arterial disease was assessed by the ankle-arm index, measured by a hand-held Doppler stethoscope. An ankle-arm index <0.9 defined peripheral arterial disease. We used algorithms based on self-reported diagnoses and/or medications to establish the prevalence of cardiovascular disease. Cardiovascular disease was defined as coronary heart disease (defined as angina, myocardial infarction, coronary artery bypass surgery, or carotid endarterectomy), congestive heart failure, or cerebrovascular disease (transient ischemic attack or stroke). For hypertension, we used self-report, medications, and measured blood pressure. Renal insufficiency was defined as creatinine clearance <40 ml/min calculated by the Cockcroft-Gault equation (18). Poor eyesight and urinary incontinence were assessed by self-report. Cognitive function was assessed by scores from the Teng Mini-Mental State Examination (19) and the Digit Symbol Substitution test of the Wechsler Adult Intelligence Scale-Revised (20).

Potential confounders

Prevalent hip and knee osteoarthritis was based on reported diagnoses and previous or current symptomatology. Depressive symptomatology was measured by the CES-D scale, using the score of ≥16 to define individuals at risk of depression (21). Smokers were considered as current, former, or never smokers. Physical activity for the 7 days before the interview

was assessed by questionnaire for intensity level and time spent climbing stairs, walking for exercise, walking for other purposes, aerobics, and weight training. The number of kilocalories per week per kilogram of body weight spent in each activity was calculated using each activity/intensity combination. The score of all activities was summed and multiplied by body weight to create an overall physical activity score in kilocalories per week.

Body composition

Body composition was hypothesized to be a mediator of the association between diabetes and subclinical functional limitation.

Weight was measured by a standard beam scale to the nearest 0.1 kg, and height (millimeters) was measured twice by a Harpenden stadiometer (Holtain, Crosswell, U.K.). Using the mean of two height measurements, BMI was calculated as weight in kilograms/height in meters squared. Total body fat (kilograms) and lean mass (kilograms) were measured by dual X-ray absorptiometry (DXA) (QDR 4500 A, software version 8.21; Hologic, Waltham, MA). The amount of lean soft-tissue mass was calculated, excluding fat and bone (22).

Statistical methods

Of the Health ABC participants, 2,926 had complete information on subclinical functional limitation and diabetes and constituted the study population for the analysis. For all of the other categorical variables with missing data, a separate category within each variable was used for missing data so that the observations remained in the analysis. Baseline characteristics of individuals with and without diabetes were compared using logistic regression after controlling for age, sex, and race. Continuous variables, including age, body composition measures, and biological measures, were compared between diabetic and nondiabetic participants using generalized linear models adjusted for age, sex, and race. Self-reported subclinical functional limitation was compared according to diabetes status and by diabetes duration, using χ^2 test and χ^2 test trend across diabetes duration categories. For the physical performance measures of subclinical functional limitation, generalized linear models and the ANOVA procedure for trend test were used to compare the means according to diabetes status and by diabetes duration. From those variables related to both diabetes and subclinical functional limitation ($P \leq 0.10$), multivariate analyses were performed to test whether the association between diabetes and subclinical functional limitation could be explained by these variables after controlling for age, sex, race, and study site. Multivariate logistic regression was used to estimate the association between diabetes and self-reported subclinical functional limitation, and multivariate polytomous logistic regression was used to study the association between diabetes and severity of subclinical functional limitation (1, 2, and 3 difficulties). Linear regression analyses were performed to assess differences in physical performance score. Comorbidities and impairments hypothesized to be potential mediators or confounders of the association between diabetes and subclinical functional limitation were added progressively to the models. When total body fat was included in the regression models, an additional adjustment was made for body height to normalize total body fat. A value of $P < 0.05$ was accepted as statistically significant in final multivariate models. To test if poorer control in diabetic individuals would influence subclinical functional limitation more in those with higher levels of HbA_{1c}, we cross-classified HbA_{1c} level ($<$ or $\geq$7%), diabetes duration (less or more than median), and diabetes status and created dummy variables for each of three categories that were then used in the fully adjusted model (n = 2,891). The reference group was the nondiabetic group with HbA_{1c} $<$7%. All analyses were performed using SAS software (SAS Institute, Cary, NC).

RESULTS — Among the 2,926 participants with complete information, 556 (19%) were diabetic at baseline with a self-reported mean duration of disease of 10.7 ± 11.7 years. Participants with diabetes were more likely to be male, black, and have a lower level of education (Table 1). The diabetic participants exhibited poorer health status across all indicators, including biological markers, and tended to have greater body weight and total fat and higher total muscle mass. In the participants with diabetes, muscle mass was also higher among those with poorer glycemic control (HbA_{1c} $\geq$7%) than among those with HbA_{1c} $<$7% ($P < 0.05$).

Table 2 presents the prevalence of subclinical functional limitation according to diabetes status and duration. Participants with subclinical functional limitation were more likely to be female and black even among diabetic participants ($P < 0.01$). Diabetic individuals had more self-reported difficulty in walking 1 mile (38%), rising from a chair (16.6%), or walking up 20 steps (36.2%) than the nondiabetic group ($P < 0.001$). In all, 53% of the diabetic participants reported difficulty with tasks defining subclinical functional limitation versus 40% of nondiabetic individuals ($P < 0.01$). Diabetic participants also showed poorer functional capacity on the objective performance measures.

Multivariate analyses

Multivariate analyses are shown in Table 3. Compared with those without diabetes, after adjustments for age, sex, and race, diabetic individuals continued to exhibit a higher prevalence of subclinical functional limitation with an odds ratio (OR) of 1.70 (95% CI 1.40–2.06). The association between diabetes and subclinical functional limitation was weakened by adjustments for body composition, diabetes complications, and potential confounders (Table 3, models 2–4) but still remained significant. Controlling for these covariates decreased the excessive risk of subclinical limitation by 43% in diabetic individuals. Obesity and diabetes-related comorbidities accounted for most of the attenuation of the association between diabetes and subclinical functional limitation. When further adjusted for glycemic control and diabetes duration in the final model, poor glycemic control among the diabetic population was associated with subclinical functional limitation in the group with higher diabetes duration (1.53 [1.11–2.11]) and in those with lower diabetes duration (1.63 [1.16–2.30]) compared with the nondiabetic population with HbA_{1c} $<$7%.

The association between diabetes and subclinical functional limitation was stronger with increased severity of subclinical functional limitation (Table 3). Participants with diabetes were 32% more likely to have one difficulty, 45% more likely to have two difficulties, and 69% more likely to have three difficulties compared with those without diabetes after adjustment for body composition, comorbidities, and confounders.

Table 1—*Characteristics by diabetes status*

	Diabetes	No diabetes	*P**
n (%)	556 (19)	2,370 (81)	
Sociodemographic			
Males	55.9%	46.9%	†
Blacks	56.7%	38.7%	†
Age (years)	73.6 ± 2.9	73.6 ± 2.9	NS
Education <12 years	26.0%	21.5%	‡
Diabetes severity			
Treatment (%)			
Number of medications taken	6.5 ± 3.9	5.5 ± 4	†
Any hypoglycemic medication	64.4%	—	
On insulin	17.1%	—	
On oral hypoglycemics	47.6%	—	
Blood examination			
Fasting glucose (mg/dl)	153.8 ± 54.9	93.3 ± 10	†
HbA_{1c} (%)	7.8 ± 1.5	6 ± 0.6	†
Triglycerides (mg/dl)	166.9 ± 105.7	132.3 ± 76.1	†
Diabetes-related comorbidities			
Cerebrovascular disease	9.6%	7.5%	NS
Coronary heart disease	26.7%	18.2%	†
Congestive heart failure	5.7%	2.2%	†
Hypertension	65.2%	48.1%	†
Peripheral arterial disease	6.3%	4.6%	NS
Renal insufficiency	5.1%	4.4%	NS
Poor eyesight	25.0%	19.3%	†
Urinary incontinence	42.7%	37.2%	‡
Systolic blood pressure	137.8 ± 21.4	135.5 ± 21.0	‡
Diastolic blood pressure	69.2 ± 11.5	71.8 ± 11.7	†
Lowest ankle-arm index	1.04 ± 0.2	1.07 ± 0.2	†
Cognitive function			
Teng Mini-Mental Score	89.4 ± 8.9	90.2 ± 8.2	‡
Digit symbol substitution score	34.0 ± 14.2	35.3 ± 14.8	‡
Potential confounders			
Osteoarthritis	11.5%	9.6%	NS
Depression	4.6%	4.6%	NS
Current smokers	7.4%	10.0%	‡
Physical activity (kcal/week)	943.1 ± 2,001	1,062.2 ± 1,844	NS
Body composition			
Weight (kg)	80.7 ± 14.9	74.9 ± 14.8	†
BMI (kg/m^2)	29.1 ± 4.9	27.1 ± 4.7	†
Total fat (kg) (DXA)	28.1 ± 9.1	25.5 ± 8.5	†
Total lean soft-tissue (kg) (DXA)	50.0 ± 9.6	47.1 ± 10.0	†

Data are means ± SD unless otherwise indicated. NS, not significant. *P values from age/sex/race-adjusted logistic regression or linear models comparing individuals with and without diabetes. †$P < 0.01$; ‡$P < 0.05$

Participants with diabetes also showed worse physical performance (β −0.18; $P < 0.001$). Diabetes continued to be associated with poorer performance after controlling for total body fat, comorbidities, and confounders. Poor glycemic control among the diabetic population was also associated with poorer physical performance scores in the higher diabetes duration group.

A comparison of newly diagnosed diabetic individuals (defined by fasting glucose ≥126 mg/dl, $n = 113$) with those without diabetes ($n = 2,370$) showed no association between new diagnosis of diabetes and subclinical functional limitation.

Multivariate analysis conducted specifically among diabetic participants showed that self-reported subclinical functional limitation was associated with peripheral vascular disease, osteoarthritis, higher total body fat, depression, and poorer glycemic control ($P < 0.05$) (results not shown).

CONCLUSIONS — Findings from this study show that even in a well-functioning older population, 43% of the participants report subclinical functional limitation, and the prevalence is higher in diabetic individuals (53 vs. 40% in nondiabetic population). Among those with diabetes, these associations were only partially explained by increased total fat and by a higher prevalence of comorbidities. These findings are consistent with previous work that found a major burden of physical disability associated with diabetes in both cross-sectional and longitudinal studies among older U.S. adults (3,7,8). Various medical conditions, including diabetes, have been associated with self-reported mobility and walking disability (23–25). Other studies also have found that diabetic participants have lower physical performance scores (4,5). However, these studies included participants with more severe disabilities.

This study extends previous work by examining early indicators of functional decline, not simply limitation and disability, and found that the diabetic population also had more subclinical functional limitation than their nondiabetic counterparts. After adjustment for all comorbidities and impairments, the association between diabetes and subclinical functional limitation was reduced to a large degree but still remained statistically significant. Diabetes was still associated with a 40% increased risk of subclinical functional limitation. Increased severity of subclinical functional limitation strengthened the association between diabetes and subclinical functional limitation.

The fact that no single factor explained the association between diabetes and disability has also been found in other studies, suggesting that the mechanism causing the disability in older diabetic individuals is multifactorial (3,7,8). Several comorbidities and impairments that could be causes of disability were more prevalent among diabetic participants. Several modifiable factors, including obesity, osteoarthritis, and peripheral arterial disease, were associated with subclinical functional limitation risk among diabetic participants, consistent with other studies (7,8). All of these factors are also associ-

ated with disability in aging population studies (26).

An important advance of this study is the addition of glycemic control as a covariate. The fact that poor glycemic control in diabetic individuals was associated with subclinical functional limitation strongly suggests that diabetes severity plays an important role in the disablement process. Our findings that no association was found between newly diagnosed diabetes and subclinical functional limitation also support the role of glycemic control in the disablement process. Only one other study of physical functioning included a measure of glycemic control. In diabetic blacks, having lower fructosamine was associated with better-reported functional status. This association, however, was not independent of sensory and other medical problems (27). Poorer glycemic control is associated with protein catabolism in skeletal muscle that may lead to sarcopenia and thus loss of functional capacity. But, in our diabetic population, those with poorer glycemic control had higher muscle mass compared with those with HbA_{1c} <7%, largely due to their greater overall body weight.

Improvements in glycemic control also affect the quality of life with fewer physical symptoms, including pain and fatigue, being reported (28,29).

One limitation of our study is that we have no data on neuropathy at baseline, a common diabetes-related complication known to be a cause of disability in diabetic individuals (7,30).

Additionally, due to the study design (cross-sectional study), a causal relationship between diabetes and functional status could not be determined. Over the course of the study, we plan to look at prospective factors affecting risk of incident functional limitation with diabetes.

We found several potentially remediable factors such as obesity, osteoarthritis, peripheral arterial disease, and depression associated with subclinical functional limitation in the diabetic population. Decreasing obesity by lifestyle-based weight loss intervention, including diet and/or exercise, could improve physical function, but this has not been tested in randomized clinical trial among older diabetic individuals and may be a finding of the Look AHEAD study. Early diagnosis and treatment of diabetes-related comorbidities could prevent the

Table 2—*Subclinical functional limitation according to diabetes status*

Parameters	No diabetes	Diabetes				*P*
		All diabetic	≤5 years	6–15 years	>15 years	
n	2,370	556	245	140	135	
Self-reported subclinical functional limitation (%)						
Difficulty walking 1 mile	25.7	38	36.7	42.9	32.6	*
Difficulty rising from chair	11.6	16.6	18.4	17.9	14.1	*
Difficulty walking up 20 steps	25.9	36.2	30.6	38.6	39.3	*
Subclinical functional limitation (any self-reported difficulty)	40.3	53.2	50.6	58.6	50.4	*
One difficulty (*n* = 639)	21.5	23.4	24.1	25.7	20.7	
Two difficulties (*n* = 477)	14.9	22.3	18.0	25.0	23.7	
Three difficulties (*n* = 136)	4.0	7.6	8.6	7.9	5.9	*
Physical performance measures						
Time to complete five chair-stands (s)	14.2 ± 4	15.0 ± 4.1	14.7 ± 4.0	15.2 ± 3.9	15.1 ± 3.6	*
Walking speed over 6 meters (m/s)	1.18 ± 0.24	1.11 ± 0.23	1.14 ± 0.22	1.11 ± 0.21	1.07 ± 0.27	*†
Standing balance						
Semitandem-tandem score	3.74 ± 0.75	3.59 ± 0.97	3.71 ± 0.79	3.53 ± 1.04	3.46 ± 1.12	*†
Balance walks						
Walking speed for narrow walk (m/s)	0.96 ± 0.45	0.80 ± 0.51	0.85 ± 0.50	0.80 ± 0.49	0.73 ± 0.54	*
Summary physical performance score	2.21 ± 0.5	2.00 ± 0.6	2.08 ± 0.5	1.98 ± 0.6	1.91 ± 0.6	*†

Data are means ± SD unless otherwise indicated. Comparison diabetes versus no diabetes: *$P < 0.01$. †$P < 0.05$ for trend tested by Mantel-Haenszel χ^2 for categorical variables and ANOVA for continuous variables. NS, not significant.

Table 3—*Multivariate regression analyses for the association of diabetes with subclinical functional limitation*

Subclinical functional limitation	*n*	Model 1	Model 2	Model 3	Model 4
Any self-reported difficulty versus no difficulty	1,252	1.69 (1.39–2.06)	1.54 (1.26–1.88)	1.38 (1.12–1.70)	1.40 (1.14–1.73)
Only one difficulty	639	1.44 (1.13–1.83)	1.35 (1.06–1.72)	1.29 (1.00–1.65)	1.32 (1.02–1.69)
Two difficulties	477	1.85 (1.43–2.40)	1.66 (1.27–2.16)	1.44 (1.09–1.89)	1.45 (1.10–1.91)
Three difficulties	136	2.53 (1.69–3.78)	2.17 (1.45–3.26)	1.71 (1.12–2.61)	1.69 (1.10–2.61)
Multivariate linear regression models β coefficient for diabetes (95% CI)†					
Summary physical performance score		−0.18* (−0.22 to −0.13)	−0.14* (−0.19 to −0.10)	−0.11* (−0.15 to −0.06)	−0.11* (−0.15 to −0.07)

Data are OR (95% CI) of subclinical functional limitation for diabetes. Model 1: Age, sex, race, education, and study site. Model 2: + Body composition measures (total body fat, body height). Model 3: + Comorbidities (peripheral arterial disease, coronary heart disease, congestive heart failure, transient ischemic attack, stroke, hypertension, renal insufficiency, poor eyesight, urinary incontinence, and cognitive function). Model 4: + Potential confounders (osteoarthritis, depression, smoking, physical activity). *$P < 0.01$; †unstandardized β coefficient.

onset of mobility limitation and reduce the burden of disability associated with diabetes. Moreover, glycemic control could be a mediator in this relationship. Many older individuals with diabetes do not achieve targets for glycemic control (31,32). Adjustment for diabetes-related comorbidities reduced the association between diabetes and subclinical functional limitation to a large degree. Intensive blood-glucose control has been proved to prevent the onset and/or slow the progression of several complications in patients with type 2 diabetes, particularly microvascular complications, including retinopathy, nephropathy, and neuropathy (33–35). The association between glycemic control and self-reported subclinical functional limitation was significant whatever the diabetes duration.

Data are emerging that suggest diabetes itself independently contributes to the risk of functional limitation. Mechanisms for this deserve additional investigation, focusing especially on glycemic control. Whether efforts to better control diabetes in old age would have an impact on disability should be tested.

Data on early limitations that progress to disability are lacking at this time. Assessment of subclinical functional limitation in well-functioning older individuals is essential for identifying those at risk of disability in those with diabetes, particularly for those at a stage when interventions are likely to delay onset and progression to severe limitation or disability.

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