Hyperglycemia and Incidence of Frailty and Lower Extremity Mobility Limitations in Older Women

Rita R. Kalyani, MD, MHS, Jing Tian, MS,†‡ Qian-Li Xue, PhD,†‡ Jeremy Walston, MD,†‡ Anne R. Cappola, MD, ScM,§ Linda P. Fried, MD, MPH,‖ Frederick L. Brancati, MD, MHS,# and Caroline S. Blaum, MD, MS***

OBJECTIVES: To determine the degree to which hyperglycemia predicts the development of frailty and lower extremity mobility limitations.

DESIGN: Secondary data analysis of longitudinal data collected in a prospective cohort study.

SETTING: Baltimore, Maryland.

PARTICIPANTS: Three hundred twenty-nine women from the Women's Health and Aging Study II aged 70 to 79 at baseline who had all variables needed for analysis.

MEASUREMENTS: Glycosylated hemoglobin (HbA1c) at baseline, categorized as less than 5.5%, 5.5% to 5.9%, 6.0% to 6.4%, 6.5% to 7.9%, and 8.0% and greater, was the independent variable. The incidence of frailty and lower extremity mobility limitations (based on self-reported walking difficulty, walking speed, and Short Performance Physical Battery score) was determined (follow-up ≈ 9 years). Frailty was assessed using the Cardiovascular Health Study criteria. Covariates included demographic characteristics, body mass index, interleukin-6 level, and clinical history of comorbidities. Statistical analyses included Kaplan–Meier survival curves and Cox regression models adjusted for important covariates.

RESULTS: In time-to-event analyses, HbA1c category was associated with incidence of walking difficulty ($P = .049$) and low physical performance ($P = .001$); association with incidence of frailty and low walking speed had a trend toward significance (both $P = .10$). In regression models adjusted for demographic characteristics, HbA1c of 8.0% or greater (vs < 5.5%) was associated with an approximately three-times greater risk of incident frailty and three to five times greater risk of lower extremity mobility limitations (all $P < .05$). In fully adjusted models, HbA1c of 8.0% or greater (vs < 5.5%) was associated with incident frailty (hazard ratio (HR) = 3.33, 95% confidence interval (CI) = 1.24–8.93), walking difficulty (HR = 3.47, 95% CI = 1.26–9.55), low walking speed (HR = 2.82, 95% CI = 1.19–6.71), and low physical performance (HR = 3.60, 95% CI = 1.52–8.53).

CONCLUSION: Hyperglycemia is associated with the development of frailty and lower extremity mobility limitations in older women. Future studies should identify mediators of these relationships. **J Am Geriatr Soc 60:1701–1707, 2012.**

Key words: hyperglycemia; elderly; frailty; mobility; disability

Diabetes mellitus in elderly adults is a growing public health concern, with almost two-thirds of older U.S. adults having diabetes mellitus or pre-diabetes mellitus.[1] The numbers of persons with diabetes mellitus will almost double by 2030.[2] In older people, diabetes mellitus can have a significant effect on physical functioning and has been associated with lower extremity mobility limitations.[3,4] Diabetes mellitus has also been associated with frailty, a geriatric condition of physiological vulnerability to stressors associated with adverse outcomes such as disability and mortality,[5–8] but whether hyperglycemia per se predicts the development of frailty or lower extremity mobility limitations has not been fully described.

Cross-sectional studies have previously demonstrated that hyperglycemia is associated with frailty.[9] Different dynamics of glucose and insulin in response to a glucose challenge have also been reported in frail and nonfrail women, with 2-hour post-oral glucose tolerance test (OGTT) levels of glucose and insulin better discriminating frailty status than fasting values,[8] although the direction of

From the *Divisions of Endocrinology, †Geriatric Medicine and Gerontology, ‡Center on Aging and Health, Johns Hopkins University, Baltimore, Maryland; §Division of Endocrinology, Diabetes and Metabolism, University of Pennsylvania, Philadelphia, Pennsylvania; ‖Department of Epidemiology, Mailman School of Public Health, Columbia University, New York, New York; #Division of General Internal Medicine, Johns Hopkins University, Baltimore, Maryland; and **Division of Geriatric Medicine, University of Michigan, Ann Arbor, Michigan.

Address correspondence to Rita R. Kalyani, 1830 East Monument Street, Suite 333, Baltimore, MD 21287. E-mail: rrastogi@jhmi.edu

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the association between frailty status and abnormalities in glucose metabolism remains unclear. Longitudinal associations between insulin resistance and incident frailty have been described in the Cardiovascular Health Study (CHS).[10] Nonetheless, the use of short-term fasting measures of glycemia have limited these studies, whereas biomarkers such as glycosylated hemoglobin (HbA1c), which reflect exposure to glucose over the past 3 months and are influenced by fasting and postprandial hyperglycemia, may be less variable. Hyperglycemia has also been found to be cross-sectionally associated with lower extremity disability[4,9] but to the knowledge of the authors of the current study, associations between hyperglycemia and declines in lower extremity mobility function over time have not been previously explored.

The goal of the present study was to describe the association between hyperglycemia and incident frailty and lower extremity mobility limitations in a longitudinal cohort of older, community-dwelling women. The hypotheses were that hyperglycemia (assessed according to HbA1c) would predict the development of frailty and lower extremity limitations; that the association between hyperglycemia and frailty and lower extremity limitations would be independent of potential confounders; and that the association between hyperglycemia and frailty and lower extremity limitations would be nonlinear.

METHODS

Subjects

The study population consisted of women aged 70 to 79 at baseline enrolled in the Women's Health and Aging Study II who represented the two-thirds least disabled women living in the community.[11] Four hundred thirty-six women were enrolled at baseline and assessed at seven study visits from 1994 to 2008; 382 had information on HbA1c levels available at baseline. After excluding participants with missing covariates (n = 11), stroke or Parkinson's disease (more likely to have lower extremity limitations due to primary disease; n = 5), or HbA1c levels less than 4.5% (n = 2), 364 women remained. The excluded women did not differ significantly from those included in the study.

For incident frailty analysis, women who had the outcome (frailty) at baseline (n = 11), missing outcome (frailty) status at baseline (n = 2), or no follow-up (n = 22) were also excluded, leaving 329 women available for this analysis. The total number of participants who completed study visits was as follows: two visits (n = 25), three visits (n = 58); four visits (n = 22); five visits (n = 26); six visits (n = 74); and all seven visits (n = 124).

Similar exclusion criteria were used for lower extremity outcomes, which resulted in the following analytical samples to examine incidence of self-reported walking difficulty (n = 329); low walking speed, defined as a level in the lowest quartile (<0.82 m/s) for the study population (n = 259); and low physical performance, defined as a Short Physical Performance Battery (SPPB) score in the lowest quartile (<9) for the study population (n = 267).

Variables

The main outcome was frailty as described by Fried and colleagues.[5,6] Five criteria were used: shrinking (body mass index (BMI) <18.5 kg/m^2 or $\geq$5% annual weight loss), weakness (low grip strength), poor endurance (exhaustion), slowness (low walking speed), and physical inactivity. Those with no criteria were categorized as nonfrail, one or two criteria as prefrail, and three or more criteria as frail.

Lower extremity mobility outcomes included subjective and objective measures. Participants self-reported any difficulty walking one-quarter of a mile at all visits. Walking speed was calculated based on a usual-pace 4-m measured walk test at all visits. Assessment of the SPPB, consisting of chair stands, walk test, and tandem stands for balance, was available for all visits except visit 4, and scores were calculated using criteria defined previously and adapted for clinical use.[12–14]

The main exposure of interest was HbA1c. Nonfasting blood samples were obtained and HbA1c measured using a BioRad assay (Hercules, CA) from frozen whole blood.[9]

Demographic information was obtained using a standardized questionnaire. Height and weight were measured to calculate BMI. BMI was categorized according to World Health Organization criteria as underweight (<18.5 kg/m^2), normal (18.5–24.9 kg/m^2), overweight (25.0–29.9 kg/m^2), and obese ($\geq$30 kg/m^2).[15] For the analysis of incident walking difficulty only, underweight was categorized as less than 20 kg/m^2, because all women with BMI less than 18.5 kg/m^2 developed walking difficulty. Interleukin (IL)-6 was measured from frozen serum using a commercial enzyme-linked immunosorbent assay (Quantikine Human; R&D Systems, Minneapolis, MN). History of diabetes mellitus, coronary artery disease, osteoarthritis and chronic obstructive pulmonary disease was self-reported. Coronary artery disease included congestive heart failure, myocardial infarction, and angina pectoris.

Peripheral arterial disease was defined as an ankle–brachial index less than 0.9.[3] Peripheral neuropathy was defined according to physician report or inability to feel the complete vibration of a 128 Hz tuning fork in either great toe.

Statistical Analysis

Baseline characteristics were compared according to incident frailty status using the chi-square test or Student *t*-test. Incidence was defined as first occurrence of each event in all analyses. Kaplan–Meier survival curves explored the association between HbA1c (categorized to account for potential nonlinear relationships into <5.5%, 5.5–5.9%, 6.0–6.4%, 6.5–7.9%, $\geq$8.0%) and time to event for frailty and lower extremity outcomes. HbA1c categories were chosen based on previous studies suggesting greater risk of mortality at the highest and lowest thresholds,[16,17] with cutoffs for the intermediate categories based on diagnostic criteria for diabetes mellitus.[18] Cox regression models for discrete time outcomes were constructed to characterize the independent association between HbA1c at baseline and outcomes in the following sequential models: Model 1: adjusted for demographics (age, race,

education), Model 2: adjusted for Model 1 plus BMI, Model 3: adjusted for Model 2 plus IL-6, Model 4: adjusted for Model 3 plus comorbidities (coronary artery disease, osteoarthritis, chronic obstructive pulmonary disease, peripheral arterial disease, peripheral neuropathy). For the frailty model, sensitivity analyses were performed adjusting for prefrailty status at baseline. Potential quadratic associations between HbA1c and incident frailty or other outcomes were explored in regression models, but because none were found, the lowest HbA1c category (<5.5%) was chosen as the reference for all analyses. The statistical program used was SAS 9.2 version (SAS Institute, Inc., Cary, NC).

RESULTS

Seventy-seven of 329 women (23%) developed incident frailty during a mean follow-up of 8.6 ± 3.6 years. Within the baseline nonfrail cohort, 70 women (21.3%) died, and 57 (17.4%) dropped out before frailty development. The women who did and did not develop frailty were similar with respect to age, race, and education (Table 1). A significant difference in the distribution of BMI categories was found between groups ($P = .01$), with a greater proportion of women being obese or underweight in the group that developed frailty. Not surprisingly, a greater proportion of women were prefrail at baseline in the incident frailty group than in the nonfrail group (55.8% vs 29.4%; $P < .001$). There were no significant differences in the clinical history of other comorbidities (all $P > .05$). Inflammatory markers (IL-6) were largely similar, whereas mean HbA1c tended to be higher in women who developed incident frailty (6.2%) than in those who did not (6.0%, $P = .07$).

For lower extremity limitations, 27% of women developed self-reported walking difficulty (mean follow-up 8.4 ± 3.7 years), 63% of women developed low walking speed (mean follow-up 8.8 ± 3.5 years), and 67% developed low physical performance (mean follow-up 8.8 ± 3.5 years). The overall incidence rate for frailty and lower extremity limitations during follow-up per 100 person-years was 2.26 (95% confidence interval (CI) = 1.78–2.83) for frailty, 2.78 (95% CI = 2.24–3.42) for walking difficulty, 8.46 (95% CI = 7.20–9.88) for low walking speed, and 8.61 (95% CI = 7.40–9.97) for low physical performance.

Kaplan–Meier survival curves were next examined for time-to-event analyses (Figure 1A–D). The women were divided into the following HbA1c categories for incident frailty analysis: less than 5.5% (n = 64), 5.5% to 5.9% (n = 135), 6.0% to 6.4% (n = 77), 6.5% to 7.9% (n = 38), and 8.0% or greater (n = 15). Similar HbA1c categories were used for lower extremity outcomes. HbA1c category was associated with probability of developing frailty ($P = .10$) and low walking speed ($P = .10$), although the results were not statistically significant based on the log-rank test (Figure 1A, C). Nevertheless, HbA1c category was significantly associated with probability of developing incident walking difficulty (Figure 1B, $P = .049$) and low physical performance (Figure 1D, $P = .001$).

The association between HbA1c category and incident frailty was further explored in regression models (Table 2).

Table 1. Selected Baseline Participant Characteristics According to Development of Frailty During Follow-Up

Characteristic	All, N = 329	Incident Frailty During Follow-Up: Yes, n = 77	Incident Frailty During Follow-Up: No, n = 252	*P*-value[a]
Demographic				
Age, mean ± SD	73.9 ± 2.8	74.0 ± 2.9	73.9 ± 2.8	.62
White,%	83.9	83.1	84.1	.83
Education, years, mean ± SD	12.6 ± 3.3	12.2 ± 2.9	12.8 ± 3.4	.17
Body mass index, kg/m^2 (%)				
<18.5	3.3	6.5	2.4	.01
18.5–24.9	36.2	29.9	38.1	
25.0–29.9	38.9	31.2	41.3	
≥30.0	21.6	32.5	18.3	
Mean ± SD	26.6 ± 5.1	27.3 ± 5.5	26.4 ± 4.9	.16
Clinical history,%				
Prefrailty	35.6	55.8	29.4	<.001
Osteoarthritis	66.9	66.2	67.1	.89
Chronic obstructive pulmonary disease	23.4	26.0	22.6	.54
Coronary artery disease	13.7	16.9	12.7	.35
Peripheral arterial disease	4.6	7.8	3.6	.12
Peripheral neuropathy	7.0	7.8	6.8	.76
Known diabetes mellitus	7.6	9.1	7.1	.57
Laboratory measure				
Interleukin-6, pg/mL, mean ± SD	3.9 ± 4.8	4.2 ± 7.0	3.8 ± 3.9	.49
Glycosylated hemoglobin (%)				
<5.5%	19.5	15.6	20.6	.24
5.5–5.9%	41.0	40.3	41.3	
6.0–6.4%	23.4	24.7	23.0	
6.5–7.9%	11.6	10.4	11.9	
≥8.0%	4.5	9.1	3.2	
Mean ± SD	6.0 ± 0. 9	6.2 ± 1.1	6.0 ± 0.8	.07

BMI = body mass index; SD = standard deviation.

[a] Comparing participants with incident frailty to those without incident frailty.

HbA1c of 8.0% or greater was significantly associated with incident frailty after adjusting for demographic characteristics (hazard ratio (HR) = 3.63, 95% CI = 1.41–9.33; Model 1) compared to the reference category (HbA1c < 5.5%). This association was slightly attenuated after further adjustment for BMI and IL-6 but essentially unchanged. After adjustment for comorbidities, the association remained significant (HR = 3.33, 95% CI = 1.24–8.93; Model 4). In sensitivity analyses, prefrailty was further adjusted for in the fully adjusted model to explore its contributions as a potential confounder;[9] the association was attenuated such that it was no longer significant (HR = 2.64, 95% CI = 0.95–7.34). However, prefrailty may also contribute as a mediator of the association between HbA1c and incident frailty in women who are nonfrail at baseline.

HbA1c of 8.0% or greater was also associated with significantly more difficulty in walking after adjustment for

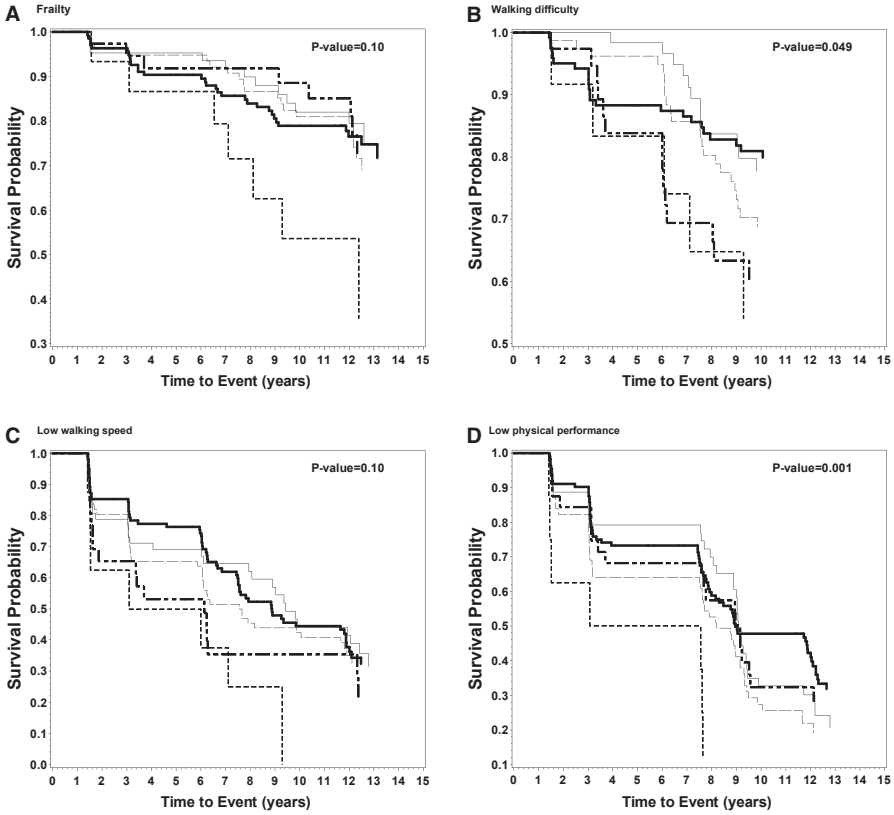

Figure 1. Kaplan–Meier curves demonstrating the time to event of outcomes during follow-up for older women categorized according to level of baseline glycosylated hemoglobin (HbA1c): <5.5% (thin solid line ——), 5.5–5.9% (thick solid line ▬▬), 6.0–6.4% (thin dashed line — —), 6.5–7.9% (thick short and long dashed line ▬ ▪), and ≥8% (thick short dashed line ▪ ▪). The association between HbA1c category and probability of survival for the outcomes are (A) frailty ($P = .10$); (B) self-reported walking difficulty ($P = .049$); (C) slow walking speed ($P = .10$); and (D) low Short Physical Performance Battery score ($P = .001$). The *x*-axis shows the time to event in years. The *y*-axis shows the probability of survival.

demographic characteristics (HR = 5.03, 95% CI = 1.91–13.27; Model 1) compared to the reference category (Table 2). This association was moderately attenuated but remained significant after adjustment for BMI (HR = 2.93, 95% CI = 1.08–7.96; Model 2), IL-6 (HR = 2.91, 95% CI = 1.07–7.91; Model 3), and comorbidities (HR = 3.47, 95% CI = 1.26–9.55; Model 4). HbA1c of 6.5% to 7.9% was also significantly associated with incident walking difficulty in models adjusted for demographic characteristics (HR = 2.26, 95% CI = 1.05–4.87; Model 1), suggesting a possible graded association between HbA1c level and incident walking difficulty, although this was no longer statistically significant in fully adjusted models (Model 4).

Similarly, HbA1c level of 8.0% or greater was associated with development of low walking speed after adjustment for demographic characteristics (HR = 3.14, 95% CI = 1.35–7.34; Model 1), BMI (HR = 2.89, 95% CI = 1.23–6.81; Model 2), IL-6 (HR = 2.70, 95% CI = 1.15–6.33; Model 3), and comorbidities (HR = 2.82, 95% CI = 1.19–6.71) compared to HbA1c <5.5%.

Last, HbA1c of 8.0% or greater (versus reference) was associated with development of poor physical performance after adjustment for demographic characteristics (HR = 3.31, 95% CI = 1.43–7.69), BMI (HR = 3.25, 95% CI = 1.38–7.66), IL-6 (HR = 3.09, 95% CI = 1.31–7.28), and comorbidities (HR = 3.60, 95% CI = 1.52–8.53).

DISCUSSION

Participants in the highest HbA1c category (≥8.0%) had a statistically significantly three times greater risk of developing frailty and three to five times greater risk of developing lower extremity mobility limitations after adjustment for demographics than those in the lowest category (<5.5%). The association between HbA1c and incident frailty and lower extremity mobility limitations remained independent of potential confounders and was nonlinear, with most events occurring in the highest HbA1c category (≥8.0%), suggesting that hyperglycemia, particularly in the diabetic range, can predict the onset of incident frailty and lower extremity mobility limitations less than a decade later.

To the knowledge of the authors, the association between hyperglycemia and incident frailty has been explored in only one other study.[11] In that study, homeostasis model of insulin resistance (HOMA-IR) was calculated based on fasting glucose and insulin. For every standard deviation increment in HOMA-IR, the adjusted HR for frailty was 1.15 (95% CI = 1.02–1.31). In comparison, the current study found that the association between HbA1c and incident frailty was nonlinear. An advantage of HbA1c is that postprandial hyperglycemia, which may be more related to frailty status than fasting

Table 2. Frailty and Lower Extremity Mobility Limitations in the Women's Health and Aging Study II, According to Glycosylated Hemoglobin at Baseline

	Adjusted Hazard Ratio (95% Confidence Interval)			
Glycosylated Hemoglobin Level,%	**Model 1**	**Model 2**	**Model 3**	**Model 4**
Frailty				
5.5–5.9	1.28 (0.65–2.49)	1.35 (0.69–2.65)	1.30 (0.66–2.55)	1.29 (0.65–2.55)
6.0–6.4	1.18 (0.57–2.45)	1.26 (0.59–2.67)	1.25 (0.59–2.65)	1.25 (0.58–2.69)
6.5–7.9	1.17 (0.44–2.81)	1.05 (0.41–2.7)	1.01 (0.39–2.61)	1.04 (0.40–2.70)
≥8.0	3.63 (1.41–9.33)	3.16 (1.19–8.35)	3.12 (1.18–8.27)	3.33 (1.24–8.93)
Difficulty walking one-quarter of a mile				
5.5–5.9	1.10 (0.59–2.05)	1.18 (0.63–2.21)	1.17 (0.62–2.20)	1.14 (0.60–2.15)
6.0–6.4	1.36 (0.71–2.61)	1.25 (0.64–2.43)	1.24 (0.64–2.41)	1.28 (0.65–2.51)
6.5–7.9	2.26 (1.05–4.87)	1.70 (0.77–3.75)	1.70 (0.77–3.75)	1.77 (0.79–3.97)
≥8.0	5.03 (1.91–13.27)	2.93 (1.08–7.96)	2.91 (1.07–7.91)	3.47 (1.26–9.55)
Low walking speed[a]				
5.5–5.9	1.04 (0.67–1.61)	1.06 (0.68–1.66)	1.04 (0.67–1.63)	1.02 (0.65–1.59)
6.0–6.4	0.95 (0.59–1.53)	0.98 (0.60–1.59)	0.91 (0.56–1.49)	0.93 (0.56–1.52)
6.5–7.9	1.25 (0.69–2.28)	1.24 (0.67–2.29)	1.12 (0.60–2.09)	0.97 (0.52–1.82)
≥8.0	3.14 (1.35–7.34)	2.89 (1.23–6.81)	2.70 (1.15–6.33)	2.82 (1.19–6.71)
Low physical performance[b]				
5.5–5.9	0.99 (0.66–1.50)	1.01 (0.67–1.54)	1.00 (0.66–1.53)	0.97 (0.63–1.49)
6.0–6.4	1.23 (0.78–1.93)	1.24 (0.79–1.96)	1.19 (0.75–1.89)	1.19 (0.75–1.88)
6.5–7.9	1.14 (0.64–2.02)	1.13 (0.63–2.02)	1.05 (0.58–1.88)	1.06 (0.58–1.92)
≥8.0	3.31 (1.43–7.69)	3.25 (1.38–7.66)	3.09 (1.31–7.28)	3.60 (1.52–8.53)

Model 1 adjusted for age, race, education. Model 2 adjusted for variables in Model 1 and body mass index. Model 3 adjusted for variables in Model 2 and interleukin-6. Model 4 adjusted for variables in Model 3 and clinical history of comorbidities (osteoarthritis, chronic obstructive pulmonary disease, coronary artery disease, peripheral arterial disease, and peripheral neuropathy).

[a] Walking speed in the lowest quartile (<0.82 m/s).

[b] Short Performance Physical Battery score in the lowest quartile (<9).

levels alone, also influences levels.[8] The other advantages of HbA1c are that it can be obtained without fasting and may be less variable with repeat testing.[19] Thus, the results of the current study provide a new perspective on a previously described relationship between hyperglycemia and incident frailty.

It has been demonstrated that higher HbA1c levels are cross-sectionally associated with walking difficulties.[9] The present study reports for the first time that the development of difficulty in self-reported walking or performance-based measures of lower extremity function is greater in persons with HbA1c levels of 8.0% or greater than in those with levels less than 5.5% at baseline, independent of confounders. Objective measures may also detect preclinical limitations that predict future disability.[12,14]

Evidence was not found of a J-shaped association between HbA1c and incident frailty or lower extremity outcomes, although such associations have been described between HbA1c and mortality.[16,17,20] Explanations for this discordance include the potential relationship between hypoglycemia and sudden death [21] unrelated to the presence of frailty. Furthermore, frailty events occurring right before death may have been undetected in the analyses, yet when the composite outcome of incident frailty or death was examined, the results were unchanged (data not shown), although smaller numbers of participants with high HbA1c levels in the current study may have limited the ability to detect quadratic associations.

The association between hyperglycemia and incident frailty may be due to several factors. Similar to other studies, the current study found that frail women were more likely to be obese, which may be associated with chronic inflammation.[22] Inflammation is further associated with lower leg muscle mass and strength, which in turn is related to functional impairment, physical disability, and frailty.[12,23,24] Lower muscle function is inherent in the definition of frailty. In addition, chronic hyperglycemia is a risk factor for cardiovascular disease, which in turn has been associated with frailty,[25] although the current study found that hyperglycemia was related to incident frailty status independent of the potential contributions of adiposity, inflammation, and cardiovascular disease. It also found that participants with hyperglycemia were more likely to develop lower extremity mobility limitations independent of confounders and that associations were independent of potential mediators such as peripheral arterial disease and peripheral neuropathy.[3]

A possible implication of these findings is that direct pathways linking hyperglycemia to muscle loss need to be considered. Insulin resistance and diabetes mellitus have been associated with excessive loss of lean body mass and muscle strength in observational studies.[26,27] Insulin resistance is also associated with skeletal muscle mitochondrial dysfunction,[28] which may suggest underlying pathways for these epidemiological findings, but further studies are needed.

Limitations of this study include the small sample size of participants in the highest HbA1c category (≥8.0%), although it was possible to discern significant associations between HbA1c and incident frailty and lower extremity mobility limitations in adjusted regression models. The study included only women, limiting generalizability. There was also high mortality, probably because of the old

age of the women, although these occurred nonsystematically (data not shown). Only baseline HbA1c levels were explored, although changes in HbA1c levels over time may contribute to frailty status as well. Furthermore, the majority of persons with HbA1c of 8.0% or greater had a known history of diabetes mellitus, so it was not possible to separate the effect of HbA1c from the presence of diabetes mellitus itself. As a result, the possibility that other aspects of the diabetic state, such as the use of glucose-lowering therapies, could contribute to frailty or that higher HbA1c levels in older persons reflects poorer self-care management and greater risk of adverse outcomes cannot be excluded. Lastly, although the study focused on an individual measure (HbA1c), recent studies have suggested that deficits across multiple systems may be most important in frailty development.[29] It is likely that complex interactions between dysglycemia and abnormalities in other physiological systems contribute to the pathophysiology of frailty, which it is hoped will be explored in a future study. Strengths of the current study include the well-characterized Women's Health and Aging Study II cohort, use of standardized protocols, inclusion of self-reported and performance-based measures of lower extremity function, examination of potential nonlinear relationships, and length of follow-up. Furthermore, use of a long-term glycemic marker (HbA1c) minimized potential variability in exposure.

In conclusion, this study adds to growing evidence that hyperglycemia is independently associated with the development of frailty and with incident lower extremity mobility limitations. HbA1c testing may represent a practical method to screen individuals at high risk for the development of adverse geriatric outcomes, but whether this greater risk of adverse geriatric outcomes is primarily related to HbA1c levels in the moderately uncontrolled diabetic range or higher ($\geq$8.0%) needs to be further explored. A better understanding might provide insight into whether clinical guidelines proposing less-aggressive HbA1c targets in older adults with diabetes mellitus are appropriate.[30] Although the mechanism remains unclear, direct associations between hyperglycemia and muscle loss may contribute and should be investigated in future studies. Intervention studies are ultimately needed to explore whether treatment of hyperglycemia may delay or prevent the development of frailty and lower extremity limitations in older adults.

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