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Editorial

Frailty, Sarcopenia and Diabetes

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It is estimated that 26.9% of persons 65 years and older in the United States have diabetes mellitus (www.cdc.gov/diabetes/pubs/estimates11.htm).[1] A systematic review has shown that persons with diabetes are at increased risk of mobility disability and disability in instrumental activities of daily living and activities of daily living.[2] Frailty has been defined as a predisability state, which increases the vulnerability of a person to have a poorer outcome (eg, disability, hospitalization, nursing home placement, or death) when exposed to a stressor.[3,4] The major cause of frailty is sarcopenia. Modern definitions have redefined sarcopenia as lacking muscle strength, as measured by gait speed or grip strength, in the presence of a low muscle mass.[5–8] In this review, we explore the relationship of frailty and sarcopenia to diabetes mellitus.

Frailty

The viability of frailty as a clinical tool was strongly enhanced by the development by Fried et al[9,10] of the physical frailty phenotype model. This model has been validated in multiple studies as being an excellent predictor of poor outcomes.[11–14] It consists of 5 components:

- Exhaustion
- Physical activity
- Walking speed
- Grip strength
- Weight loss

A person with any 3 of these is considered frail, and with 1 or 2 is considered prefrail. The Study of Osteoporotic Factors model is a simpler model with 3 components,[15] which is also well validated for producing unfavorable outcomes.[16,17]

A competing model is that developed by Rockwood and colleagues[18–21] using the Canadian Health Study. In its simplest form it represents the addition of all the deficits (illnesses) the person has, with the larger score indicating a greater likelihood of the person being frail. This is more a comorbidity index than a unique index of frailty.

Recently a simple screening questionnaire with components of both the approaches described previously has been developed that takes less than 15 seconds to do (Table 1). This index, known as the FRAIL, has been validated in Australia,[22–24] Hong Kong,[11] the United States,[16,25] and Europe.[26,27] It is highly predictive of adverse outcomes even when persons who have functional deficits are excluded.[16,25]

Another set of frailty questionnaires includes psychosocial variables.[28–31] These measure cognitive frailty, which is briefly discussed at the end of this article.

Frailty and Diabetes

At 65 years or older, diabetic individuals are more likely to be frail than nondiabetic older adults (Table 2).[32–34] The frailty prevalence of 32% to 48% in persons with diabetes older than 65 is much higher than the 5% to 10% seen in the general population.[35–38] In persons 55 years and older, frailty is still common in diabetic individuals but much less so than in the older group.[39,40]

All the studies found that frail diabetic individuals had a higher mortality than nonfrail diabetic individuals.[32–41] These studies suggest that persons older than 55 with diabetes should be screened for frailty and, when present, should have their frailty treated.

Frail persons are more likely to have glucose dysregulation during a glucose tolerance test.[42] The ideal level of glucose control for a frail diabetic patient has not been established, although consensus panels have suggested an HbA_1C between 7.5% and 8.0%.[43–45] A single trial with vildagliptin attempted to determine the optimum glucose-lowering effect in frail compared with nonfrail diabetic individuals.[46] In this study, individualized HbA_1C targets were set by investigators who knew the frailty status of the patients. Unfortunately, the end HbA_1C targets were similar in both frail and nonfrail patients, not allowing a determination of an optimum glycemic target for older diabetic patients.[47]

Overall, the management of frailty requires a focus on decreasing sarcopenia (vide infra). In a small study, Pariser et al[48] examined the effects of the “Active Steps for Diabetes” program on type 2 diabetes and frailty. They found the program lowered HbA_1C and reduced frailty in persons using a walker. This is in concert with numerous

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Table 1
The Frail Scale: A Rapid, Validated Scale for the Detection of Frailty

3 or more positive answers: frail
1 or 2 positive answers: prefrail
Fatigue (have felt tired most or all of the time in past 4 weeks)
Resistance (have difficulty or unable to climb a flight of stairs)
Aerobic (have difficulty or unable to walk a block)
Illness (have more than 5 illnesses)
Loss of weight (have lost more than 5% of weight in past 6 months)

studies in generalized frail communities suggesting that exercise can decrease frailty.[49]

Besides focusing on sarcopenia, the treatment of frailty has 3 other elements:

(1) Management of treatable causes of fatigue: People with diabetes have higher levels of fatigue and this is related to increased complications.[50] Treatable causes of fatigue include vitamin B12 deficiency, hypoadrenalism, hypothyroidism, anemia, sleep apnea, hypotension, syncope, and depression. Treatment of sleep apnea in diabetic individuals results in lower blood pressure, better glycemic control, and an improvement in quality adjusted life years.[51] Depression is more common in diabetic individuals and psychological and pharmacological interventions positively affect depression and improve glycemic control.[52] Diabetes is commonly associated with autonomic neuropathy, which leads to orthostatic hypotension, arrhythmias, and syncope.[53]
(2) Management of polypharmacy: Older persons with diabetes are likely to be on many medicines. Polypharmacy has been identified as a major cause of frailty and disability in older persons.[54] Anticholinergic medicines can cause cognitive decline and frailty.[55] Overtreatment of blood pressure results in hypotension and falls.[56] Statins can lead to myopathy in older persons and this should be looked for by measuring an aldolase as well as a creatine phosphokinase.[57] Hypoglycemia can further aggravate frailty.[58]
(3) Management of weight loss: Although in younger persons weight loss is a cornerstone of treatment for type 2 diabetes mellitus, in older persons, in general, including diabetic individuals, weight loss has been shown to be associated with accelerated mortality.[59] Weight loss leads to a loss of muscle and bone, increasing frailty, falls, and hip fractures. There are numerous treatable causes of weight loss; for example, depression, medications, dysphagia, dental problems, nosocomial infections (tuberculosis and *Helicobacter pylori*), hyperthyroidism, hypercalcemia, pheochromocytoma, malabsorption (celiac disease, pancreatic insufficiency), eating problems (tremors), shopping problems, therapeutic diets, and cholecystitis.[60] There is evidence that caloric supplements, which should be given between meals, can improve outcomes.[61] Finally, it should be recognized that frailty may occur due to weight loss associated with the Sodium Glucose Transporter inhibitors and other antidiabetic drugs (eg, alpha-1-glucose inhibitors) that can cause weight loss.[62]

Sarcopenia and Diabetes

Muscle loss occurs at the rate of 1% per year after 30 years of age.[63] Excessive muscle loss has been called sarcopenia and leads to functional deterioration.[64] Aging also is associated with a decrease in gait speed[65] and handgrip strength.[66] The new definitions for sarcopenia, which include low walking speed or grip strength, as well as low muscle mass, have been shown to be better at predicting adverse outcomes compared with low muscle mass alone.[67–69]

Kim et al,[70] in studying 414 men 65 years or older, found that in men, low muscle mass, defined by appendicular muscle mass/height^2 was lower in diabetic than in nondiabetic individuals. The data were less clear in women, but muscle quality (total skeletal mass/weight) was lower in diabetic individuals in both sexes. In another study in Korea of 610 individuals, sarcopenia was present in 15.7% in patients with diabetes and 6.9% in the control group.[71] Leenders et al[72] found that both appendicular skeletal mass and leg extension strength was lower in individuals with type 2 diabetes mellitus compared with normoglycemic controls. In middle-aged Asian Indians, skeletal mass was lower in diabetic than nondiabetic individuals.[73]

In the Hertfordshire (UK) cohort study of 1391 persons aged 60 to 70 years, there was a significant reduction in grip strength in persons with diabetes.[74] In the Health, Aging and Body Composition Study cohort consisting of 1840 persons aged 70 to 79 years, diabetic individuals had greater declines in muscle mass and leg muscle strength and poorer muscle quality over 3 years.[75] Thigh muscle cross-sectional area declined twice as fast in older women with diabetes than in their nondiabetic counterparts over 6 years. Mid upper arm muscle area and handgrip strength are lower in diabetic compared with nondiabetic individuals who have undergone coronary artery bypass.[76] Impaired mobility has been shown to be associated with reduced lower extremity muscle strength in persons with type 2 diabetes.[77] Gait speed is reduced in persons with diabetes.[78] Data from the National Health and Nutrition Examination Survey (1999–2002) found that persons with diabetes had reduced quadriceps strength and power, as well as a reduced gait speed.[79]

In diabetic rats, there is fiber atrophy with a relative increase in fast oxidative/glycolytic (Type IIA) fibers and a decrease in slow oxidative (Type I) fibers.[80] This muscle atrophy with a switch to glycolytic fibers also has been seen in humans with diabetes.[81–83] There is also a marked decrease in muscle capillary density.[84] In

Table 2
Prevalence of Frailty in Persons With Diabetes Mellitus

Author	*n*	Age, y	Scale	% Diabetes			Outcome
				Control	Prefrail	Frail	
Ottenbacher et al[32]	2049	65+	Fried	24	31	32	Predicted mortality and frailty at 10 years
Hubbard et al[33]	2305	65+	7-point scale	42.2	—	43.4	Frail had shorter survival
Cacciatore et al[34]	1288	65+	FSS*	40.2	—	48.4	Frail had higher mortality at 12 years
Bouillon et al[39]	2707	55 ± 5	Fried	7.4	11.2		—
Tang et al[40]	3257	55+	Frailty Index Men	12.8	—	9.8	Frailty Index predicts diabetes
			(Rockwood) Women	18.6	—	20.3	
Lee et al[38]	3018	65+	Fried	Not reported			Women with diabetes had worse outcomes over 2 years

Dashes, no data available.
*Frailty staging system (functioning, disability, mobility, cognition, vision, hearing, incontinence, social support).