

Diabetes, Sarcopenia, and Frailty

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Persons who have diabetes mellitus tend to have an accelerated aging process [1,2] that places them at greater risk for developing frailty at an earlier age [3–10]. Frailty can be defined simply as a condition in which an older person is coping just above the disability threshold, but any stressor (either physical or psychologic) is liable to cause the person to become disabled or need intensive long-term physical therapy to allow recovery to the pre-disability state [6]. Rockwood and colleagues [11–13] have stressed that frailty really is the sum total of the number of illnesses a person has resulting in a physical decline. An objective definition of frailty created by Fried and her colleagues [14] has been validated and includes five components:

- Unintentional weight loss (10 pounds within the last year)
- Self-reported exhaustion
- Weakness (grip strength)
- Slow walking speed
- Low physical activity

The International Academy of Nutrition Health and Aging has operationalized the definition of frailty combining components of both Rockwood's and Fried's definitions [15,16] in the acronym "FRAIL":

Fatigue

Resistance (cannot climb one flight of stairs)

Ambulation (cannot walk one block)

Illnesses (more than five)

Loss of weight (< 5% over 1 year or less)

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Overall, the presence of frailty depends on deterioration in muscle and nerve function, anemia, declining cardiopulmonary reserve, and loss of executive function [15,16]. Diabetes mellitus tends to cause problems in each of these areas. Insulin resistance is a key factor in the failure of many of these systems [17] and has been shown to relate to excess disability in nursing home residents [18]. Loss of homeostasis occurs commonly in diabetic persons and leads to vulnerability, a construct similar to that of frailty. In the end, frailty results in increased institutionalization, hospitalization, and mortality.

Falls, fractures, and frailty

Falls are a common problem in frail older persons. In the study of osteoporotic fractures of 9249 women, 18% of women fell more than once a year [19]. Non-insulin-treated diabetics had an age-associated increased risk of falls (odds ratio, 2.78), as did insulin-treated diabetics (odds ratio, 1.668). Diabetics who fell had more falls than nondiabetics. In the non-insulin-dependent diabetic women, the increased falls could be explained by an increase in factors known to increase the risk for falls. This was not the case for falls in insulin-dependent diabetics. Tilling and colleagues [20] found that the incidence of falls in older persons who had diabetes was 39%. Risk factors for falls in this group were poor diabetic control, needing assistance with mobility, and a prior cerebrovascular accident. In the Women's Health and Aging Study, women who had diabetes also had a higher propensity for falling and for having more than one fall compared with women who did not have diabetes [21]. Risk factors for falls included musculoskeletal pain, insulin therapy, obesity, and poor lower extremity performance. Miller and colleagues [22] found that older diabetic persons were at increased risk for both falls and injurious falls.

In a nursing home study, 35% of residents fell during a period of 299 days. The incidence of falling was 78% for diabetics and 30% for nondiabetics. Only abnormal gait and balance and diabetes independently predicted falls [23].

Patients who have type 1 diabetes have poor bone formation related to the decreased anabolic effects of insulin [24]. Therefore these patients are more likely to be osteopenic. Patients who have type 2 diabetes tend to have higher bone mineral density, although thiazolidinediones have been shown to produce osteopenia [25]. Despite greater bone mineral density, women who have type 2 diabetes mellitus have an increased risk of fracture.

Bonds and colleagues [26] studied 93,676 postmenopausal women in the Women's Health Initiative Observational Cohort. They found that women who had diabetes had an increased odds ratio of fractures of 1.20 after correcting for fall frequency. In nearly 3000 women between the ages of 70 and 79 years, diabetes mellitus carried an elevated risk of fracture of 1.64 after correcting for risk factors for fracture [27]. Those who experienced

fracture had lower bone mineral density and lean mass, reduced peripheral sensation, an increased incidence of stroke, and more falls.

A major risk factor for hip fracture in older persons is vitamin D deficiency [28–30], which is associated with osteopenia and also with increased falls [31,32]. Recent studies have clearly shown the vitamin D needs to be replaced aggressively when 25-hydroxy (25[OH]D) vitamin D levels are less than 30 ng/mL [33–37]. Vitamin 25(OH)D levels decline longitudinally with aging [38]. Vitamin D levels are lower in diabetics than in nondiabetics [39].

Testosterone levels in older males often are in the hypogonadal range [40–43]. Men who have diabetes have lower testosterone and bioavailable testosterone levels than do nondiabetic men [44,45]. Low testosterone levels are associated with increased falls and hip fractures [46,47]. Testosterone replacement therapy increased muscle mass and strength, bone mineral density, and function [48–51].

Two important causes of falls in older diabetics that often are overlooked are orthostasis and postprandial hypotension [52–54]. All older diabetics should have their blood pressure measured while standing. Aggressive treatment of orthostasis is important, and these patients may need treatment with midodrine or fludrocortisone. Postprandial hypotension occurs when a meal releases vasodilatory peptides such as calcitonin gene-related peptide, resulting in falls, syncope, and/or myocardial infarction [55]. The alpha-1-glucosidase inhibitors release glucagon-like peptide 1 which slows gastric emptying [56]. Slowing the rate of gastric emptying decreases the fall in blood pressure following a meal [57]. Both miglitol and acarbose can be used to decrease postprandial hypotension [58].

Osteoporosis is poorly recognized and treated by physicians [59,60]. In diabetics there is a need to look actively for osteoporosis and provide aggressive treatment with calcium, vitamin D, and bisphosphonates [61–64]. Elderly women who have diabetes mellitus may be resistant to bisphosphonates [65].

Sarcopenia

Diabetic patients tend to have worse function than nondiabetics [22,66–68]. This impairment is associated with a decline in muscle function. Persons who have diabetes mellitus, particularly when associated with renal failure, have accelerated loss of muscle function [68–71]. Different factors predict loss of muscle mass and decline in muscle strength [72].

Sarcopenia is the age-related decline in muscle mass [73]. It has been defined operationally as appendicular lean mass divided by height squared [74]. Sarcopenia is associated with increased disability and mortality [75]. Fat infiltration into muscle can be demonstrated by attenuation on muscle MRI [76]. This fat infiltration is termed “myosteatosis” and may play a major role in the decline in muscle strength with aging. Persons who have excess fat and sarcopenic muscles—the sarcopenic obese or “fat frail” patients—have very high levels of disability and mortality [77].

The causes of sarcopenia are multifactorial (Table 1) [78]. Free fatty acid accumulation within tissue leads to abnormalities in phosphorylation of the insulin receptor substrate and function of the glucose transporter receptor [79]. This accumulation can occur because of abnormalities in mitochondria or increased circulating triglycerides. Altered glucose metabolism leads to decreased muscle strength.

Diabetes is associated with peripheral neuropathy and a decrease in motor end plates [80]. Motor end plates play an important role in maintaining muscle mass and coordinating muscle contraction. Thus, their loss plays an important role in the pathogenesis of loss of muscle function.

Anabolic hormones are important in the maintenance of muscle mass by activating the phosphatidylinositol-3-kinase–active human protein kinase system in the cell [81]. Insulin resistance decreases the activity of this pathway. Growth hormone increases insulin growth factor-1 (IGF-1) that plays a major role in increased protein synthesis and decreased protein catabolism. A gene-splice variant of IGF-1 called “mechanogrowth factor” plays an important role in stimulating satellite cells and repair of motor units [82].

The decline in IGF-1 in diabetic animal models results in a sixfold increase in atrogene activation with a subsequent increase in proteolysis [83]. Increasing IGF-1 levels restored the atrogenes to normal levels.

Testosterone and dehydroepiandrosterone sulfate are both related to muscle mass and strength [84–87]. The low levels of bioavailable testosterone in diabetic and ageing men play an important role in the loss of muscle mass and strength [88–90]. Besides direct effects on protein synthesis, possibly by increasing IGF-1, testosterone also stimulates stem cells to produce satellite

Table 1
Factors involved in the pathogenesis of sarcopenia

Factor	Effect of aging	Effect of diabetes	Major systems altered
Motor end plates	Decrease	Decrease	Coordinated muscle contraction
Insulin growth factor-1	Decrease	Decrease	Protein synthesis
Mechanogrowth factor	Decrease	Unknown	Satellite cell formation
Ghrelin	Uncertain	Decrease	Anorexia and growth hormone
Testosterone	Decrease	Decrease	Protein synthesis and satellite formation
Myostatin	Unknown	None	Inhibits satellite cell formation and proteolysis
Proinflammatory cytokines	Increase	Increase	Proteolysis and apoptosis
Angiotensin	None	Increase	Cleaves actinomycin
Oxidative metabolism	Decrease	Increase	Oxidative damage
Food intake	Decrease	Increase	Muscle and fat
Creatine/branched chain amino acids	Decrease	Decrease	Protein synthesis
Exercise	Decrease	Mostly decrease	Protein synthesis

cells and inhibit the production of adipocytes [91]. Satellite availability is essential to allow muscle repair and to maintain muscle strength.

Ghrelin is a peptide hormone produced from the fundus of the stomach. It increases food intake, growth hormone release, and memory [92,93]. Ghrelin levels are lower in persons who have type 2 diabetes mellitus, suggesting a possible role for ghrelin in the regulation of muscle mass [94].

Myostatin is a protein that inhibits muscle growth [95]. It both inhibits satellite cell cycling and, through cachexia-inducing factor, increases proteolysis. Its levels are not altered in diabetes [96].

Proinflammatory cytokines such as tumor necrosis factor alpha and interleukin-6 play an important role in stimulating proteolysis and apoptosis in muscle cells [97]. Cytokines stimulate proteolysis by activating muscle ring finger protein-1, which then results in activation of the ubiquitin-proteasome system (the “intracellular death chamber”). This activation leads to the formation of amino acids and small peptides that are exported from the muscle into the circulation. There is a strong correlation between interleukin-6 and muscle mass, strength, and functional status [98,99]. Persons who have diabetes have elevated cytokine levels, suggesting that cytokines play an important role in the development of the sarcopenia associated with diabetes [100].

Diabetes results in elevated angiotensin II levels [101]. Angiotensin II activates caspases that cleave actin from myosin. This cleavage represents the first step in muscle breakdown. Cleavage of actin from myosin is essential before these proteins can undergo proteolysis by the ubiquitin-proteasome system. Angiotensin-converting enzyme inhibitors are associated with increased strength [102].

Diabetes has elevated levels of oxidative metabolism [103] that can lead to liposomal damage of the cells and apoptosis. In addition, declining levels of phosphocreatine reduce energy transfer from the mitochondria. Creatine replacement together with exercise increased muscle strength in older persons [104,105].

Weight loss caused by poor nutritional status leads to muscle wasting [106,107]. With aging there is a physiologic anorexia of aging that places older persons at risk of developing severe weight loss and muscle atrophy when they have a superimposed disease [108–113]. Maintenance of muscle mass requires relatively high protein intake on the order of 1.2 to 1.5 g/kg [114]. Because of fears of renal disease, diabetics often receive too little protein in their diet. Branched-chain amino acids such as leucine play an important role in the maintenance of protein synthesis because they stimulate mammalian target of rapamycin, which increases the rate of protein synthesis and decreases lysosomal activity.

Muscle hypoxia plays an important role in sarcopenia. Atherosclerosis decreases blood flow to the leg muscles resulting in decreased strength and exercise capacity [115,116]. Anemia occurs commonly in older persons, especially in those who have some degree of renal failure [31,106,117–119].

Immobility and decreased physical activity play a major role in the loss of muscle activity. Disuse activity occurs rapidly in older persons at bed rest [120]. Exercise, particularly resistance exercise, plays a key role in the maintenance of muscle mass [121–124].

Fig. 1 provides a simplified view of the biochemical changes in muscle in older diabetics that lead to the loss of muscle mass.

The treatment of sarcopenia in diabetics requires a multifocal approach, as outlined in Fig. 2.

Executive function

A decline in executive function predicts functional decline and mortality [125]. Executive function can decline acutely in persons who have delirium [126]. Diabetics can develop delirium related to hyper- or hypoglycemia

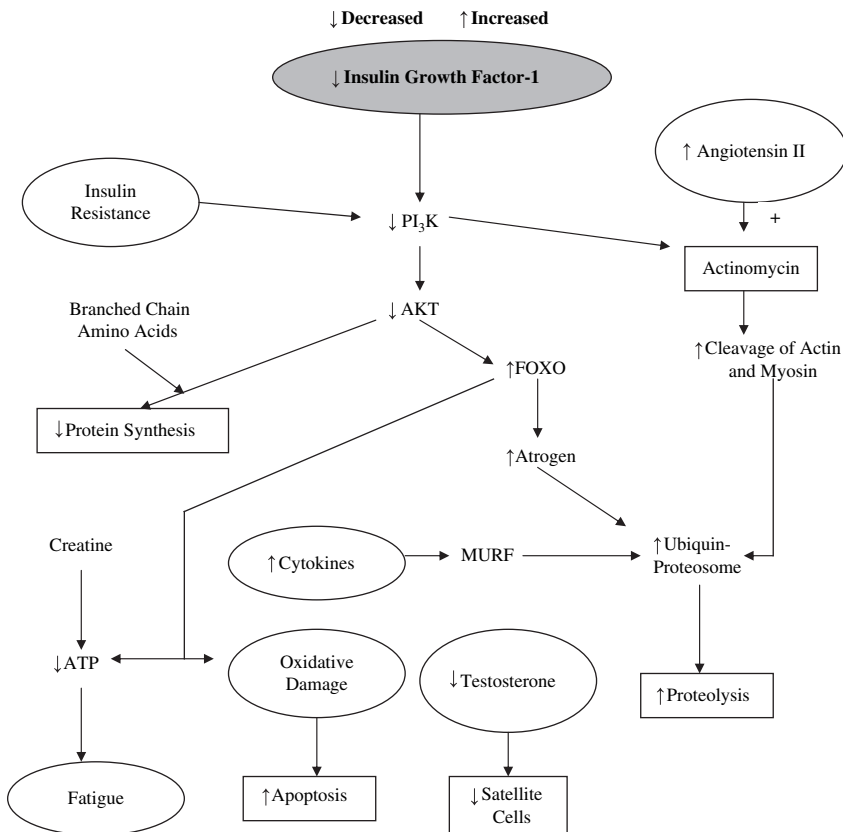


Fig. 1. Biochemical changes in muscle in diabetes. ↓, decreased; ↑, increased; KT, active human protein kinase (protein kinase-B); FOXO, forkhead protein; MURF, muscle ring finger protein; PI3K, phosphatidyl inositol-3-kinase.

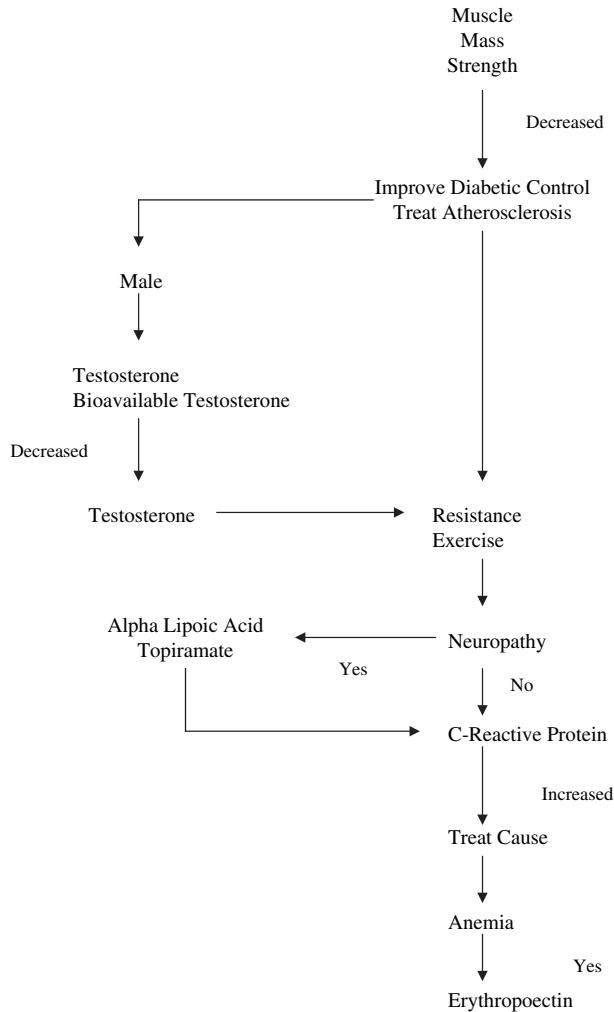


Fig. 2. An approach to the management of muscle wasting in older diabetics.

or hypertriglyceridemia [126,127] or from any of the other causes of delirium.

Numerous studies have shown that dementia occurs more commonly in diabetics than in persons who do not have diabetes [128–132]. Persons who have diabetes are at increased risk for developing vascular dementia. In addition, there is some evidence that diabetics are more likely to develop Alzheimer's disease [133,134]. The enzymes that degrade insulin also degrade amyloid beta protein [135]. It has been suggested that elevated insulin levels result in decreased degradation of amyloid beta protein. Amyloid beta protein has been shown to decrease cognition directly [136–138]. The direct effects of insulin on memory are controversial.

successfully with the Saint Louis University Mental Status examination (Fig. 3) [143,144]. This test successfully recognizes amnesic mild cognitive dysfunction as well as dementia.

The treatment of executive dysfunction in diabetes involves control of glycemia and hypertension and the use of aspirin to prevent future strokes. Drugs available to treat dementia (ie, the cholinesterase inhibitors and memantine) may help some persons, but their efficacy is limited [145–148]. Animal studies have suggested that free radical scavengers, such as alpha-lipoic acid, may improve cognition [149,150].

Summary

Frailty is a pre-disability condition. It now can be defined clinically. The major factors leading to frailty are sarcopenia and a decline in executive function. Stressors precipitate frail individuals into a state of disability. Diabetics develop the conditions necessary for frailty earlier than other aging individuals. Appropriate treatment of diabetes mellitus and frailty precursors can result in a slowing of the aging process.

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