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## Review

## Diabetes and Frailty: Two Converging Conditions?

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## ABSTRACT

Diabetes mellitus is a disabling, chronic cardiovascular and medical disease with a tremendous health, social and economic burden in our ageing communities. It has a prevalence of 10% to 30% in people older than 65 years of age, and more than half of all subjects with diabetes in the United States are older than 60 years of age.

The main impact of diabetes in older adults stems from its effect on function, both physical and cognitive, that finally impairs their quality of life, although the impact on survival is modest.

Frailty has emerged during the past 2 decades as the most powerful predictor of disability and other adverse outcomes, including mortality, disability and institutionalization in older adults.

In this article we explore the relationship between diabetes and frailty, and we recognize that they are intimately related chronic medical conditions that result in huge societal and personal health burdens.

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## R É S U M É

Le diabète sucré est une affection médicale et cardiovasculaire invalidante de longue durée qui représente un fardeau social et économique énorme en matière de santé au sein de nos communautés vieillissantes. Sa prévalence est de 10 % à 20 % chez les personnes âgées de plus de 65 ans, et plus de la moitié de tous les sujets diabétiques des États-Unis ont plus de 60 ans.

Les principales conséquences du diabète chez les personnes âgées découlent de son effet sur le fonctionnement physique et cognitif, qui finalement dégrade leur qualité de vie, bien que les conséquences sur la survie soient modestes.

La fragilité est apparue au cours des 2 dernières décennies comme le plus puissant prédicteur de l'invalidité et d'autres résultats indésirables, dont la mortalité, l'invalidité et l'institutionnalisation des personnes âgées.

Dans le présent article, nous explorons la relation entre le diabète et la fragilité, et nous reconnaissons le lien intime entre les affections médicales de longue durée et les fardeaux immenses sur la société et l'individu.

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## Introduction

Diabetes mellitus is a highly prevalent metabolic disease that can lead to marked disability. Evidence supports reduced survival in older adults with diabetes. Diabetes has a prevalence of up to 30% in persons above 65 years of age in some populations (1–4), and more than half of all people with diabetes in the United States are older than 60 years of age (4). It is estimated that as much as 40% of people who have diabetes have not been diagnosed (5). Men and women with diabetes diagnosed at age 60 have estimated

reductions in life expectancy of 7.3 to 9.5 years and good quality of life of 11.1 to 13.8 years, respectively (6).

The burden of diabetes is high and has been ranked as the seventh and eighth causes of years of life lost and disability-adjusted life years (DALYs), respectively, in Western societies, and there was an increase of more than 60% in 2010 as compared with 1990. Taking into account that 1) the ageing of the population is involved in generating the increase in DALYs due to noncommunicable diseases; 2) there is a shift to the burden in older ages; and 3) there is a tendency to a greater weight placed on years lived with disability in determining DALYs. Therefore, it is predicted that an increasingly relevant role of diabetes in older adults in the burden of disease will occur (7,8).

Thus, function becomes of great importance in the care of older people with diabetes. A key strategy is to prevent the functional

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decline instead of attempting to recover lost function. This focus on prevention stems from 2 generalized observations: to recover functional independence when disability has been developed is rather unlikely (9); and it is possible to prevent incident disability's intervening in some conditions that predict the risk for disability (10). In addition, in 2014 the results of Lifestyle Interventions and Independence for Elders (LIFE) study were published (11) and showed that direct interventions in frail older people, based on an exercise and an education program, successfully improved the physical conditions of these patients. This new approach in the quest for successful ageing results in a new challenge for the management of older patients.

Threats to functional status in older age include medical comorbidities, other chronic conditions, such as dementia and diabetes, and the onset of frailty. Frailty has emerged during the past 2 decades as the most powerful predictor of disability and other adverse outcomes, including mortality, disability and institutionalization in older adults (12). As a consequence, frailty is becoming 1 of the central issues in the assessment of older adults in clinical scenarios (13). It is described as a state of increased vulnerability to stressors that result from decreased physiologic reserve in multiple systems that cause limited capacity to maintain homeostasis (14). The prevalence of frailty in older adults has been described to be between 7% and 30% in differing population studies, depending on the nature of the populations and the criteria used (15).

Although several mechanisms are involved in the pathophysiology of frailty, all of them appear to converge in a final common pathway toward frailty, with sarcopenia as an important contributor. Sarcopenia is the loss of muscle mass associated with ageing. Its prevalence ranges from 8% to 50% in older people (16,17).

It is known that diabetes accelerates loss of muscle mass, a process that may be exacerbated by sarcopenia and frailty (18), but research has not yet delved deep enough into the close relationship among these 3 entities. The hypothesis of this short review is that diabetes, frailty and sarcopenia are related conditions, and the objectives are to explain the nature of this relationship. Is diabetes a direct factor in the development of frailty? Is sarcopenia an intermediate step in the progression of diabetes to frailty? Or are both statements true? Unless indicated specifically, this review involves all older subjects with diabetes, although we must accept that research findings in older persons with type 1 diabetes is limited.

## Diabetes Mellitus

Diabetes is a syndrome characterized by chronic hyperglycemia and disturbances of carbohydrate, fat and protein metabolism that is associated with an absolute or relative deficiency in insulin secretion and/or insulin action. The development of type 2 diabetes in older adults represents the progressive worsening of multiple age-related metabolic disturbances plus a contribution from environmental, genetic and behavioural factors (19).

At a functional level, numerous studies have found that persons with diabetes have greater functional decline than older counterparts; this is associated with disability, morbidity, mortality and institutionalization (20). Diabetes is also considered an independent risk factor in older people for falling and developing hip fractures (21).

Older individuals with diabetes have higher rates of premature death and of coexisting illnesses, such as hypertension, heart disease, cerebrovascular disease and stroke, than those without this condition (22), and they are also at greater risk for several common geriatric syndromes, such as polypharmacy, depression, cognitive impairment, urinary incontinence, injurious falls and persistent pain (23). Older patients with diabetes have increased prevalence of cognitive decline and are more likely to develop vascular dementia and possibly Alzheimer disease (20,24).

We also know that diabetes is a risk factor for developing frailty, more than doubling the risk (odds ratio [OR]: 2.18) after 3.5 years of follow up. Overall, it is associated with a decline in quality of life and a decrease in leisure activities (25,26).

## Sarcopenia

Sarcopenia describes one of the most noticeable changes that occur with ageing; it is a progressive decline of muscle mass, leading to low and impaired strength and functioning. Although there is general agreement that older people tend to become sarcopenic, there is substantial disagreement about the criteria that should be used for the definition of sarcopenia (27).

Sarcopenia affects all older people and does not discriminate on the basis of ethnicity, gender or wealth. After 50 years of age, muscle mass is reported to decline at an annual rate of approximately 1% to 2%, accelerates to as much as 1.5% to 3% per year after age 60, and becomes ever faster after age 75 (28). During ageing, the loss of muscle mass and strength is hypothesized to be due to progressive atrophy (decrease in myofibre cross-sectional area), loss of muscle fibres (29) and reduction in muscle quality due to the infiltration of fat and other noncontractile material such as connective tissue, as well as to changes in muscle metabolism and insulin resistance (30). The loss of muscle mass is due primarily to a decrease in the number of both type I (slow twitch) and type II (fast twitch) muscle fibres and a reduction in the size of the remaining muscle fibres, with a preferential atrophy of the type II fibres (31).

Intimately linked to the decrease in muscle mass, there is a metabolic deregulation, which includes a reduction in insulin sensitivity, impaired oxidative defence and decreased mitochondrial function. Sarcopenia may be associated with a severe metabolic state that is characterized by increased insulin resistance, diabetes and hypertension. Sarcopenia is used interchangeably to describe age-related muscle loss and the clinical condition. The main effect of the loss of muscle mass is reduced muscle strength and power, which are important factors in maintaining stability and gait and are necessary to the performance of the activities of daily living (32).

Increased clinical and epidemiologic interest in sarcopenia is related to the hypothesis that age-related loss of muscle mass and strength results in functional limitations and decreased mobility in older adults (33). Impaired muscle strength is highly predictive of incident disability and all-cause mortality in this population, and in older sarcopenic persons, a pathology-induced supplementary muscle weakness can very rapidly lead to disability and additional morbidity. Several epidemiologic studies have documented an association between low skeletal muscle mass and the risk for physical disability (33), and some authors have put forward the hypothesis that sarcopenia is an integral component of frailty (34).

## Frailty

As previously stated, frailty is a complex clinical entity characterized by the imbalance of homeostatic capacity, which becomes particularly evident as the inability to regain stable homeostasis after a stressful destabilizing event.

Although agreement between a standardized definition and an empirical basis is lacking (35), Linda Fried and colleagues defined a clinical phenotype of frailty, which is identified by the presence of 3 or more of the following components (36):

- Weight loss: unintentional loss of  $\geq 4.5$  kg in the past year
- Weakness: hand-grip strength in the lowest 20% quintile at baseline, adjusted for sex and body mass index
- Exhaustion: poor endurance and energy, self-reported from the Center for Epidemiologic Studies Depression scale

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