Physical Disability in the Elderly with Diabetes: Epidemiology and Mechanisms

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Abstract Diabetes mellitus is a common chronic condition worldwide, especially in the elderly population. Several epidemiologic studies in the last 2 years have consistently associated diabetes with physical disability, a condition that may profoundly affect the quality of life of older people. Although in older people with diabetes, the pathogenesis of functional limitation and disability has not been completely elucidated, it is certainly complex and involves multiple potential pathways. In this narrative review, we described the most recent epidemiologic and clinical evidence supporting the association between diabetes and impaired physical function in older persons focusing on emerging biological mechanisms explaining the excess risk of disability associated with diabetes.

Keywords Type 2 diabetes · Aging · Epidemiology · Physical disability · Elderly · Mechanisms

Introduction

Type 2 diabetes, the most common metabolic disease in older people, is highly prevalent in industrialized countries. Because of the ongoing demographic transition and progressive aging of the overall population, its prevalence will further increase in the next few decades [1], leading to different clinical presentations and different age-related complications. Indeed, in addition to the traditional cardiovascular complications, diabetes has been associated with excess risk of clinical conditions typical of the geriatric population such as physical disability that may profoundly affect the quality of life of older

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patients with this disease [2••]. Disability represents a major risk factor for loss of independence, recurrent hospitalization, falls, injuries, acute illnesses, and eventually institutionalization [3]. Despite the growing interest on the pathogenesis of diabetes-related disability, the biological mechanisms explaining this association are not completely understood.

This narrative review outlines and discusses epidemiological evidence for a causal association between diabetes and physical disability, focusing on hypothesized pathogenetic pathways that would explain the excess risk of disability associated with diabetes.

Epidemiology of Diabetes

According to the International Diabetes Federation, about 366 million people aged 20–79 years worldwide were estimated to have diabetes in 2011. If increasing trends continue, by 2030 some 552 million people will be affected by this metabolic condition [1]. For community-dwelling people in the United States, from 1980 through 2011, the percentage of people with diagnosed diabetes increased 167 % (from 0.6 % to 1.6 %) for those aged 0–44 years, 118 % (from 5.5 % to 12.0 %) for those aged 45–64 years, 140 % (9.1 % to 21.8 %) for those aged 65–74 years, and 125 % (8.9 % to 20.0 %) for those aged 75 years and older [4]. In 2012, an estimated 22.3 million people in the US were diagnosed with diabetes, representing about 7 % of the population [5•].

In the future, the diabetes epidemic is expected to expand; indeed, according to the US Census Bureau, total diabetes prevalence (diagnosed and undiagnosed cases) is estimated to increase from 14 % in 2010 to 21 % of the US adult population by 2050 [6].

Currently, besides the huge prevalence of people with clinically diagnosed diabetes, almost 10 % suffer from unrecognized disease, or meet a condition of impaired glucose tolerance (IGT)

that also constitutes a major public health problem, both because of its association with diabetes incidence [7] and its own association with an increased risk of poorer physical function [8].

Diabetes imposes a substantial burden on the economy in the form of increased medical costs and indirect costs from work-related absenteeism, reduced productivity at work and at home, reduced labor force participation from chronic disability, and premature mortality. The estimated US national cost of diabetes in 2012 was $245 billion, of which $176 billion (72 %) represents direct health care expenditures attributed to diabetes and $69 billion (28 %) represents lost productivity from work-related absenteeism, reduced productivity at work and at home, unemployment from chronic disability, and premature mortality [5•].

Diabetes as a Risk Factor for Physical Disability

Diabetes and the Disablement Process

According to Verbrugge and Jette, "the disablement process is a progressive, multi-step, and dynamic pathway" in which different diseases and several predisposing conditions may trigger and facilitate the onset of physical disability [9]. This representation offers a speculative interpretation of the pathogenetic mechanisms, connecting diabetes, impairments, functional limitation, and disability, providing important information on postulated determinants and mediators of the course of the process. In agreement with the original definition suggested by Nagi, functional limitation is characterized by "limitation in performance at the level of the whole organism or person," whereas disability denotes the presence of "limitation in performance of socially defined roles and tasks within a sociocultural and physical environment" [10]. In older people, the onset of disability may develop with different temporal trajectories (ie, progressive or catastrophic) and the level of difficulty may fluctuate over time and even regress.

Most traditional complications of diabetes are potentially associated with the multiple steps of the process leading to physical disability, one of the most relevant indicators of quality of life in older people. For example, amputation and blindness (impairments) may hinder from activities of daily living (ADLs), for example walking, nerve problems may put limitations on strengths and mobility activities (functional limitation), and the worsening cognitive function may impose limitations on instrumental activities of daily living (IADLs); for example managing money [11].

Diabetes and Disability

The relationship between diabetes and disability has been repeatedly investigated in the last few decades in multiple countries and different types of populations (Table 1). Globally taken, the results of these observational investigations demonstrated a constant excess rate of disability in multiple task of physical function in people with diabetes [2••]. More recently, other studies have confirmed and extended the results of the previous reports, addressing more innovative hypotheses underlying the biological relationship between diabetes and the early steps of the disablement process of older persons. For example, in a cross-sectional analysis of 835 people aged 65 and older enrolled in the InCHIANTI study, we have investigated the relationship between type 2 diabetes, lower extremity skeletal muscle characteristics, and performance in 2 objective measures of lower-extremity function, the 4-meter usual walking speed and 400-meters walking speed test. Compared with people without diabetes, participants with diabetes had worse muscle performance and were significantly slower on both the 4-meter and 400-meter walking test [12••].

In a study based on 156 patients recruited in 1 university and 4 district hospitals in the south of The Netherlands, people with diabetes mellitus, independently of the presence of polyneuropathy, were more likely to have a marked reduction in lower leg muscle strength and mobility, assessed by 6-minute walk test, a timed up-and-go test, and the Physical Activity Scale of the Elderly [13].

Among the more than 2500 adults aged 50 and older enrolled in the National Health and Nutrition Examination Survey (NHANES), diabetes mellitus was associated with significantly slower gait speed also after adjusting for demographic characteristics, weight, height, physical activity, C-reactive protein (CRP), and comorbidity [14].

A recent clinical investigation conducted on a small sample of well-functioning older men suggests that the detrimental effect of diabetes might play an important role also in the early steps of the disablement process. This study, conducted on 92 nondisabled men aged 70±1 years, found that diabetic men had a poorer performance on the sit-to-stand performance test compared with those without diabetes. Furthermore, this difference was not explained by the presence of other clinical characteristics commonly associated with diabetes, suggesting a causal and direct relationship between diabetes and functional limitation [15]. The hypothesis of a causal association between diabetes and accelerated decline in physical function is further strengthened by several investigations with prospective design, including, but not limited to, the EPESE [16] and the Study of Osteoporotic Fractures [17]. Taken together, these studies have demonstrated an independent and consistent increased risk of incident disability over time in persons without disability at study inception. A more recent study conducted on 2143 older Brazilian adults enrolled in the Survey on Health and Well-being of the Elderly Study (SABE), showed that by itself, the presence of diabetes did not increase the risk of disability or the need for assistance. However, diabetes was related to increased risks when assessed in combination with stroke [18].

Table 1 Recent epidemiologic studies estimating the risk of disability for selected domains of function, according to diabetes status

Author reference	n	Sex	Domain of function	Significant association	Statistical adjustment
Cross-sectional studies					
Leenders 2013 [15]	92	Men	Sit-to-stand test and handgrip test	Yes	Age, BMI, fasting glucose, high-density lipoprotein cholesterol, branched-chain amino acid concentration, habitual protein intake, physical activity level
Kalyani 2013 [14]	2573	Women/men	Gait speed (20-foot)	Yes	Age, race, education, sex, smoking, weight, height, physical activity, CRP, comorbidities.
Volpato 2012 [12••]	835	Women/men	4 and 400 m walking speed	Yes	Age, sex, muscular variables, BMI, ABI, CMAP, CSII, IL-6, CRP, stroke, CHD, CHF, MMSE, executive function
Izerman 2012 [13]	156	Women/men	6 min walk test, timed up and go test, Physical Activity Scale of the Elderly	Yes	No
Malhotra 2012 [47]	5000	Women/men	ADL	Yes	Walk 1/4 mile, climb 10 steps, housework, objective mobility test: walking speed, chair stands, tandem stands
Dybicz 2011 [48]	2317	Women/men	Activities of Daily Living Domain Score	No	No
Chiu 2011 [49]	5121	Women/men	ADL, IADL, Nagi strength and mobility activities	Yes	Sociodemographic factors, follow-up status, comorbidities
Chiu 2011[11]	20,433	Women/Men	ADL, IADL, Nagi strength and mobility activities	Yes	Age, sex, cohort, race, education
Martinez-Huedo 2011 [50]	7835	Women/men	ADL, IADL, mobility (climb 10 steps)	Yes	Age, sex
Chau 2011 [51]	66,813	Women/men	ADL, IADL	Yes	Age, sex, education
Prospective studies					
Andrade 2012 [18]	2054	Women/men	Severe ADL limitations	No	Age, sex, education, selected medical conditions, smoking, and marital status

The Pathway from Diabetes to Disability

In order to recommend and implement new strategies for the prevention of disabling effect of type 2 diabetes in older persons, it is fundamental to fully elucidate the underlying biological mechanism that may explain the excess burden of physical disability associated with diabetes. In older patients diabetes is associated with multiple impairments and conditions including ischemic heart disease, congestive heart failure, peripheral arterial disease, visual impairment, chronic renal disease, neuropathies, obesity, mood disorders, and cognitive decline that may justify the increased burden of disability associated with the disease [2••].

Results of observational studies that formally investigated the mediating role of traditional diabetes complications demonstrated that these conditions explain only a part of diabetes-related disability [19]. For example, in the InCHIANTI Study, chronic conditions including cardiovascular and cerebrovascular diseases, peripheral arterial disease, peripheral neuropathy, overweight, and cognitive impairments, explained about 18 % and 30 % of the association between diabetes and functional limitation in the 4- and 400-meter tests, respectively [12••].

The Biological Mechanisms

In older persons, the detrimental effect of glucose metabolism dysregulation interacts with the multisystemic pathophysiological changes of the aging process fostering multiple and often interplaying potential pathways summarized in Table 2.

The Role of Glycemic Control

One of the most challenging questions is whether in older diabetic patients a strict glycemic control would translate in a less pronounced functional decline over time. For young and adult patients with type 1 and 2 diabetes, a large number of observational and experimental studies demonstrates that, an optimal and tight glycemic control, along with adequate treatment of associated metabolic conditions (hypertension and dyslipidemia), are the cornerstones for diabetes management and long-term prevention of chronic diabetes complications. The widely accepted recommendation that all patients pursue a glycated hemoglobin (HbA1c) <7.0 % is based largely on studies, such us the UK Prospective Diabetes Study [20], which actively excluded people aged >65 years [21]. Nevertheless, in older patients only a few long-term studies

Table 2 Nonmodifiable and potentially modifiable risk factors for disability in older adults with diabetes

Nonmodifiable	• Age • Sex • Duration of diabetes • Genetic background	
Potentially modifiable	Diabetes-related comorbidities	• Poor glycemic control/intensive glycemic control • Peripheral neuropathies • Sarcopenia • Peripheral arterial diseases • Coronary heart disease • Congestive heart failure • Albuminuria/renal failure • Stroke • Visual impairment
	Diabetes-associated comorbidities	• Obesity • Low physical activity • Low-grade systemic inflammation • Oxidative stress • Cognitive impairment/dementia • Depressive symptoms • Arthritis • Falls/fractures • Widespread and lower-extremity pain

have demonstrated the beneficial effect of tight glycemic control. Furthermore, no studies have specifically assessed the effect of intensive anti-diabetic therapy on the future incidence of disability, falls, and frailty, although some observational studies reported better physical performance over time in older people with good glycemic control, compared with those with poor glycemic. The issue of whether aggressive diabetes treatment would be really beneficial and safe is particularly important in those complex patients with multiple comorbidities and reduced functional reserve that are at the highest risk of iatrogenic side effects and adverse drug reactions.

For example Kalyani et al. using data from the Women's Health and Aging Study II, showed that, among 329 older diabetic women, HbA1c of 8.0 % or greater (vs reference category: HbA1c <5.5 %) was associated with development of poor physical performance, low walking speed, difficulty in walking, and incident frailty [22•].

In the San Antonio Longitudinal Study of Aging, a group of community older people aged 71–85, who met the American Diabetes Association criteria for the diagnosis of diabetes, was followed over a 36-month period and classified as a poor control (HbA1c >7 %), or good control (HbA1c <7 %). After 18 and 36 months, lower-extremity performance, assessed by the Short Physical Performance Battery (SPPB), was better in the optimal glycemic control class than in the poorer control class [23].

Conversely, more recent trials have generated controversy regarding the effects of pursuing very low glucose levels in older diabetic patients. In a longitudinal study on 367 community-dwelling and nursing home-eligible individuals with diabetes mellitus enrolled at On Lok Lifeways, HbA1c levels between 8.0 % and 8.9 % appeared to be associated with less functional decline or death at 2 years than HbA1c levels between 7.0 % and 7.9 %. Moreover, across all outcomes (death, functional decline, and combined outcome) of the study, participants with an HbA1c level less than 7.0 % had the highest risk of poor outcomes [24•].

Indeed, some studies suggested that in older patients, aggressive diabetic treatment and strict glycemic control may increase the incidence of hypoglycemia, falls, fractures, and eventually mortality [25]. For example, in the ACCORD-MIND study [26], intensive glycemic control was not associated with substantial benefit on cognitive function after 40 months of follow-up, whereas older patients randomized to the intensive glucose lowering group experienced a significantly higher rate of hypoglycemic events and death [27]. These studies suggest that the current American Geriatrics Society guideline [28] HbA1c target of 8.0 % or less for frail elderly adults may be lower than necessary to maintain function and delay death for this vulnerable population.

Diabetes and Sarcopenia

Another potential mediator of the association between diabetes and disability may be the diabetes related loss of skeletal muscle mass and muscle strength that has been referred to as sarcopenia.

Sarcopenia, a very frequent clinical trait in the geriatric population, is strongly associated with functional decline, disability, and mortality [29•]. Therefore, it might be hypothesized as a potential mediator of the association between diabetes and disability.

Compared with those without diabetes, older diabetic patients have been reported having similar muscle mass, as a consequence of their usually excessive total body mass. Nevertheless, observational studies have suggested that older people with diabetes, despite having "adequate" skeletal muscle mass, tended to have reduced muscle quality and more rapid decline in muscle mass and lower extremity strength over time [12••, 30••]. In a recent cross-sectional analysis based on 835 participants of the inCHIANTI study, we have revealed that participants with diabetes, despite having a larger muscle calf area, had lower knee and ankle muscle strength and muscle power, as well as worse muscle quality (defined as the ratio of lower limb muscle strength over muscle area) and slower gait speed on both 4-meter and 400-meter walking tests. In the multivariate regression models, lower-limb muscle characteristics accounted for 24.3 % and 15.1 % of walking speed difference comparing diabetic and nondiabetic subjects in the 4- and

400-meter walks, respectively [12••]. These results have been recently confirmed by Leenders et al. who investigated whether differences in muscle mass and/or strength may translate to differences in functional capacity in older people with and without diabetes. In accordance with the decline in leg extension strength, they reported a substantially longer sit-to-stand time in the older patients with type 2 diabetes when compared with the normoglycemic controls [15]. These findings suggest that standardized assessment of muscle characteristics and lower-extremity function, with early detection of sarcopenia and impaired muscle quality, might prompt appropriate lifestyle or medical intervention to postpone functional decline, prevent disability, and preserve independence and quality of life of older persons with diabetes [2••].

Why older adults with diabetes tend to have greater decline of skeletal muscle mass and performance is not clear and still under investigation. Indeed, in patients with long-standing disease the presence of classic diabetes complications including peripheral neuropathy and obstructive arterial disease, might functionally impair lower limb skeletal muscles. Epidemiological studies have clearly demonstrated a strong and independent association of these 2 classic chronic complications with muscle strength and walking speed [31, 32].

Additional supposed causal pathway leading to sarcopenia and reduced muscle strength in patients with diabetes is increased muscle fat infiltration [33] that results in a loss of muscle quality and in decreased muscle density. Increased muscle fat infiltration has been associated with both reduced oxidative activity and maximal aerobic capacity and, furthermore, in epidemiological studies of older persons, fat infiltration predicted the risk of mobility disability over time [34].

Recent studies have also reported that people with diabetes have increased serum levels of inflammatory markers, including interleukin-6 and CRP that have been associated with muscle strength decline and risk of disability in several older populations [35, 36]. Lastly, limited leisure time physical activity and physical inactivity are also frequent in older people with diabetes, particularly in those affected by overweight and obesity, and therefore might contribute to the well documented age-related reduction in strength and physical performance. Regardless of the underlying mechanisms, these findings suggest that standardized assessment of muscle characteristics and lower-extremity function, with early detection of sarcopenia and impaired muscle quality, might prompt appropriate lifestyle or medical intervention to postpone functional decline, prevent disability, and preserve independence and quality of life of older persons with diabetes.

Diabetes and Physical Activity

Among older people with diabetes regular physical exercise represents a powerful tool to protect the integrity and function of skeletal muscle and to reduce the risk of disability. Several longitudinal studies, conducted in different countries and populations, suggest that physical activity may decrease the influence of diabetes on the development of disability, improving glycemic control and weight loss. For example in older Mexican Americans, physical activity moderates the rate of decline in disability and physical function over a 10–12-year period in older people with diabetes [37]. Among the more than 5000 overweight or obese adults with diabetes enrolled in the Look AHEAD study, an intensive lifestyle intervention, including weight loss and improved fitness, resulted in a 48 % reduction in the risk of loss of mobility over a 4-year period, compared with the control group [38•].

There are several long-term effects of low-level physical activity on the progression of functional disability related to diabetes. Reduction of physical activity may be a risk factor for the development of some conditions that, in turn, contribute to the onset of disability such as sarcopenia, heart disease, and peripheral arterial disease. Aerobic exercise may also improve glucose tolerance [39], preventing the onset of obesity and diabetes mellitus and their complications [40], and finally, may have a direct positive effect on the inflammatory status that has been involved in the development of sarcopenia and functional limitation [30••, 41].

Other Biological Mechanisms

An important step toward preventing diabetes-related disability is a better understanding of biomarkers that can identify older adults with diabetes, not yet disabled, but at the highest risk of becoming disabled. Accelerated atherosclerosis is a common pathway for the majority of diabetes-related complications: albuminuria and high proinflammatory cytokines have been linked to endothelial dysfunction, as well as initiation and progression of atherosclerosis [36, 42].

Among 1729 not institutionalized elderly adults with diabetes enrolled in the NHANES study, increased urinary albumin excretion was associated with functional disability, independent of chronic comorbidities, systolic blood pressure, glycemic control, renal function, total cholesterol, and chronic inflammation. Furthermore subjects with albuminuria and increased CRP values were significantly more likely to have higher odds of disability than individuals with albuminuria and normal CRP values, suggesting that the presence of subclinical inflammation may amplify the effect of albuminuria on functional disability in older diabetic adults [36]. Albuminuria and low-grade systemic inflammation, are related to cerebral atherosclerosis and lower limb arterial disease, that in turn have both been associated with slow gait speed, decreased muscle strength, and physical disability. Cerebral atherosclerosis precedes both cerebral macroangiopathy and subcortical white matter lesions. These cerebral lesions, thus, interrupt the integrity of frontal-subcortical circuits that are

associated with cognitive impairment, functional decline, and slow walking speed [43].

Regardless of the presence of overt neurological signs and brain pathology, cognitive impairment and depressive disorders are common risk factors for functional decline in older people. In the last few years a number of epidemiological and clinical studies strongly supported a causal linking between diabetes and these disabling conditions [44–46], suggesting additional biological pathways.

Conclusions and Future Directions

Diabetes prevalence increases with age and imposes a substantial burden both to patients and health care systems. The etiology of physical disability in older patients with diabetes is multifactorial. Nevertheless most of the mechanisms that have been postulated as important mediators of the disablement process are, at least partially, modifiable and should be considered as potential targets for feasible intervention program designed to buffer and reduce the level of disability related to diabetes. Estimates of the current and future burden of diabetes are important in order to allocate community and health resources, to emphasize the role of lifestyle, and to encourage measures to counteract trends for increasing prevalence.

Compliance with Ethics Guidelines

Conflict of Interest Lara Bianchi declares that she has no conflicts of interest. Giovanni Zuliani declares that he has no conflicts of interest. Stefano Volpato declares that he has no conflicts of interest.

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