Study of frailty index in elderly men with type 2 diabetes mellitus

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Introduction
Frailty is a common and growing multidimensional health and social care challenge across the world. Diabetes mellitus (DM) is one of the most important causes of morbidity and mortality in Egypt. Frailty and diabetes are inter-related. In addition, diabetes causes early-onset frailty. In this study we aimed to determine the frailty index in elderly men with type 2 DM and compare it with that in pre-elderly diabetic patients and age-matched healthy controls.

Materials and methods
Seventy male participants were included in the present study and were divided into three groups. Group I comprised 20 healthy men aged 65–75 years who were considered the control group; group II comprised 25 patients aged 50–64 years with type 2 DM; and group III comprised 25 patients aged 65–75 years with type 2 DM. Patients on insulin therapy and those with hypogonadism or hypothyroidism were excluded from the study. Frailty index was determined for all participants using Fried's five phenotypic parameters. Patients were considered frail if they fulfilled more than or equal to three parameters, prefrail if they fulfilled one to two parameters, and nonfrail if they fulfilled none of the parameters. Data were collected, analyzed, and compared between groups I and III and between groups II and III. Further, frailty index was correlated with the duration of DM and the degree of glycemic control.

Results
Seventy patients were divided into three groups. The mean age in group I was 68.50 ± 1.90 years, that in group II was 58.24 ± 4.34 years, and that in group III was 68.60 ± 2.43 years. Regarding the frailty index, in group I 17 patients (85%) were nonfrail, three (15%) were prefrail, and none were frail; in group II, four patients (16%) were prefrail, 21 (84%) were frail, and none were nonfrail; and in group III, three patients (12%) were prefrail, 22 (88%) were frail, and none were nonfrail. A statistically significant difference was noted between groups I and III, whereas no significant difference was noted between groups II and III. A significant positive correlation was found between the frailty index score and duration of diabetes and degree of glycemic control in groups II and III.

Conclusion
Diabetes and frailty are causally related. Diabetes is associated with frailty at earlier age. The duration of diabetes and degree of glycemic control correlate with the severity of frailty in both elderly and pre-elderly diabetic patients.

Keywords:
diabetes mellitus, elderly, frailty

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Introduction

Aging is an important part of human life, affecting all societies and cultures [1]. Roughly 100 000 people worldwide die each day of age-related causes [2]. Aging of the overall population is a significant driver of the diabetes epidemic [3]. Diabetes has a prevalence of 10–30% in people above 65 years of age. It is a premature aging syndrome, a cause of unsuccessful aging, and a disabling syndrome [4]. It is associated with disability, morbidity, mortality, and institutionalization [5]. Diabetic men and women diagnosed at age 60 have an estimated reduction in life expectancy of 7.3–9.5 years, and a good quality of life of 11.1–13.8 years [6]. Diabetes is the 11th most important cause of premature mortality in Egypt and is responsible for 2.4% of all years of life lost. Similarly, diabetes is the sixth most important cause of disability in Egypt [7]. Diabetic patients are at greater risk for several common geriatric syndromes such as polypharmacy, depression, cognitive impairment, urinary incontinence, infections, pressure ulcers, and falls and hip fractures in the elderly [8]. The disease is also associated with a decrease in leisure

activities, a decline in quality of life, and an increase in the requirement of healthcare [4]. Current standards of diabetes care do not specify a different approach to frailty in a setting of diabetes [9]. It has been proposed that diabetes in aging patients may be associated with frailty at an earlier stage than in nondiabetic counterparts [10,11].

Frailty is described as a state of increased vulnerability to stressors that results from decreased physiological reserve in multiple systems that causes limited capacity to maintain homeostasis [12]. The prevalence of frailty in the elderly has been described to be between 7 and 30% in different population studies [11]. It has been reported that frailty is a state associated with major adverse health and social events, including mortality, disability, institutionalization, and dependency [13]. Although frailty is more prevalent in older people and in those with multiple medical conditions, it can exist independently of age, disability, or disease and may be an independent physiologic process involving multiple systems [14]. Fried *et al.* [15] proposed that the factors involved in aging include neuromuscular abnormalities, deregulation of the neuroendocrine system, dysfunction of the immunological system, and a cycle of frailty. The main components would be chronic malnutrition, sarcopenia, decline in physical activities, and totally consumed energy. The result is a loss of functional capacity and limited energy reserve at a cellular level and in day-to-day activities [16,17]. Hormones are key regulators of human muscle metabolism, and age-related hormonal changes are important biological contributors to skeletal muscle decline, with an accelerated loss of muscle mass and frailty [18]. Total testosterone declines at the rate of ~1% per year in men as they age, and this is associated with a decline in muscle mass and strength, bone mineral density, and cognition. Also, a number of symptoms of frailty, such as fatigue, are associated with low testosterone levels [19]. In addition, it has been described that low testosterone levels are associated with insulin resistance and that testosterone treatment may reduce insulin resistance [20,21]. Other hormones involved in frailty are dehydroepiandrosterone [22], insulin-like growth factor-1 [23], and 25-hydroxyvitamin D [24]. All have been shown to decline with aging. Thyroid hormone derangement as a part of physiological changes of aging plays a role in the pathogenesis of frailty. Hypothyroidism and hyperthyroidism are associated with a decline in muscle strength and cognitive dysfunction and thus can produce frailty [25].

There are different diagnostic criteria for frailty, with no consensus in the literature as to the most adequate markers for its identification. However, Fried *et al.* [15] defined a clinical phenotype of frailty identified by the presence of three or more of the following components [26]:

(i) Weight loss: unintentional loss of 4.5 kg or more in the past year;
(ii) Weakness: assessed by hand-grip strength and adjusted for sex and BMI;
(iii) Exhaustion: self-reported poor endurance and energy;
(iv) Slowness: based on the time needed to complete a series of functionally important tasks (adjusted for sex and height); and
(v) Low physical activity level: lowest quintile of kilocalories of physical activity during the last week, measured with the Minnesota Leisure Activity Scale.

Diabetic patients tend to have worse function than nondiabetic individuals, which is associated with an accelerated decline in muscle function. The metabolic changes in diabetes result in changes in the connective tissue and structure of a muscle [26,27]. Skeletal muscle weakness, which is a key component of frailty and muscle dysfunction, can be influenced by both fatty infiltration of muscle tissue, insulin resistance, increased levels of cytokines, and increased levels of adiponectin [27,28]. Motor endplates play an important role in maintaining muscle mass and coordinating muscle contraction. Diabetes is associated with peripheral neuropathy and a decrease in motor endplates, leading to loss of muscle function [28,29]. The conditions necessary for frailty develop faster in diabetic patients than in other aging individuals; therefore, appropriate treatment for diabetes mellitus (DM) and frailty precursors can slow down the aging process [29,30].

It has been hypothesized that diabetes and frailty are inter-related [6] and that diabetes can cause premature frailty. We aimed in the present study to determine the frailty index in elderly men with type 2 DM and compare it with that in pre-elderly diabetic patients and age-matched healthy controls.

Materials and methods

The present study included 70 men who attended the Geriatric Outpatient Clinic, Moustafa Kamel Military Hospital, during the period from November 2014 to July 2015. Participants were divided into three groups. Group I included 20 healthy men aged 65–75 years as a control group; group II included 25 patients with type 2 DM aged 50–64 years; and group III included 25 patients with type 2 DM aged 65–75 years. Patients on insulin therapy, patients with chronic systemic diseases such as hepatic or renal diseases, and those

with hypothyroidism or hypogonadism were excluded from the study. The purpose and benefit of the study were explained to all participants, and informed written consent was obtained. The proposal was approved by the ethical committee of the Faculty of Medicine, Alexandria University.

A detailed medical history was taken from each participant of groups II and III with special emphasis on onset, duration, and treatment of DM. Blood samples were collected from all participants and sent for basic laboratory investigations, including assessment of serum thyroid stimulating hormone and free testosterone hormone levels. Frailty index was determined for all participants; patients were classified as frail if they fulfilled three or more of the following parameters, prefrail if they fulfilled one or two parameters, and nonfrail if they fulfilled none of the following parameters [15,30].

(1) Weight loss: self-reported unintentional weight loss of 4.5 kg or more in the previous year.
(2) Weakness (i.e. low hand-grip strength): determined by grip strength of the dominant hand (mean of three measurements) using a Jamar hand-held dynamometer. The patient holds the dynamometer in the hand to be tested, with the arm at right angles and the elbow by the side of the body. The base should rest on the first metacarpal, and the handle should rest on the middle of four fingers. When ready the patient squeezes the dynamometer with maximum isometric effort, which is maintained for about 5 s. No other body movement is allowed. The patient should be strongly encouraged to give maximum effort. The cutoff points adjusted for BMI were ≤32 kg for BMI>28, ≤30 kg for BMI 24.1–28, and ≤29 kg for BMI≤24.
(3) Poor endurance (i.e. self-reported exhaustion): evaluated using two statements from the center for epidemiological studies depression Scale: (a) 'I felt that everything I did was an effort' and (b) 'I could not get going'. The patients tested positive for poor endurance if they fulfilled at least one condition for 3 days or more during the last week.
(4) Slowness: evaluated using the timed get up and go test that requires the patient to stand up from a chair, walk a distance of 6 m, turn around, return, and sit down again. It thus serves as an assessment of dynamic balance. Balance function is observed and scored (normal value 17 s).
(5) Low physical activity level: participants who reported not performing daily leisure activities such as walking or gardening and/or some sport activity per week were categorized as physically inactive.

Data were collected and coded and then entered into an IBM compatible computer using the StatView software version 5.1 for windows (SAS, Inc.). Qualitative variables were expressed as number and percentage. Quantitative variables were expressed as minimum and maximum as well as mean and SD. Exact tests such as Fisher's exact and the Monte Carlo were also applied. Non-normally distributed quantitative data were analyzed using nonparametric tests such as the Mann–Whitney test and the Kruskal–Wallis test. Pearson's coefficient was used to analyze the correlation between the different parameters. Statistical significance was considered at P less than or equal to 0.05.

Group III was compared with their age-matched controls in group I, and group II was compared with group III. Frailty index was correlated with the duration of diabetes in groups II and III, and also with the glycemic control state.

Results

A total of 70 men were included in the present study. Participants were divided into three groups according to their age. The age range in group I was 65–72 years, with a mean of 68.50 ± 1.90 years; the age range in group II was 50–64 years, with a mean of 58.24 ± 4.34 years; and the age range in group III was 65–73 years, with a mean of 68.60 ± 2.43 years (Table 1).

In group II, 11 patients (44%) had been diabetic since 5–10 years, with a mean of 8.09 ± 1.22 years; eight patients (32%) had been diabetic since 11–15 years, with a mean of 13.63 ± 1.30 years; and six patients (24%) had been diabetic since more than 15 years, with a mean of 22.67 ± 1.75 years. In group III, five patients (20%) had been diabetic since 5–10 years, with a mean of 9.00 ± 1.23 years; 11 patients (44%) had been diabetic since 11–15 years, with a mean of 13.00 ± 1.27 years; and nine patients (36%) had been diabetic since more than 15 years, with a mean of 23.67 ± 4.27 years. No statistically significant difference regarding the duration of diabetes was noted between the two studied groups.

Frailty index score showed the following results: in group I, 17 patients (85%) were nonfrail, three (15%)

Table 1 Distribution of the studied groups according to age (years)

Groups	Number	Range	Mean ± SD	Significance (P)	t
I	20	65–72	68.50 ± 1.90	>0.001*	10.407
II	25	50–64	58.24 ± 4.34		
III	25	65–73	68.60 ± 2.43	0.881	0.150

P value for the Student t-test; *Significant at $P \leq 0.05$.

were prefrail, and none were frail; in group II, four patients (16%) were prefrail, 21 (84%) were frail, and none were nonfrail; and in group III, three patients (12%) were prefrail, 22 (88%) were frail, and none were nonfrail. There was significant difference between groups I and III (t = 13.40, P<0.001), but there was no significant difference between groups II and III (t = 1.213, P = 0.231) (Table 2).

A significant positive correlation was found between the frailty index score and duration of diabetes and degree of glycemic control in groups II and III (Table 3).

Discussion

Aging is characterized by diverse deleterious changes in cells and tissues that are responsible for the increased risk for morbidity and mortality [31]. Frailty is a common clinical syndrome in older adults that carries an increased risk for poor health outcomes including falls, incident disability, hospitalization, and mortality [32]. The factors implicated in the pathogenesis of frailty include endocrine changes and inflammatory cytokines [22–25]. DM is a common condition in older individuals; diabetic patients tend to have an accelerated aging process that places them at greater risk for developing frailty at an earlier age [33]. In the present study, we investigated the correlation between frailty parameters and DM in elderly and pre-elderly men. Seventy men were included in this study and were divided into three groups. There was a statistically significant difference in the frailty index between group III (mean age 68.60 ± 2.43 years) and group I (mean age 68.50 ± 1.90 years), indicating the impact of DM on elderly diabetic patients. Also, a positive significant correlation was found between the duration of diabetes, degree of glycemic control, and frailty index in such patients. In group II (mean age 58.24 ± 4.34 years), 21 patients (83%) were frail, whereas only four patients (16%) were prefrail, and none were nonfrail, indicating the deleterious effect of diabetes in this age group causing early-onset frailty.

In accordance with our results is the study by Park *et al.* [34] that included 3075 diabetic adults aged 70–79 years. Muscle strength was lower in men with diabetes. Also, longer duration of diabetes and poorer glycemic control were associated with poorer muscle strength.

Cetinus *et al.* [35] studied hand-grip strength in 76 middle-aged, diabetic patients with a mean age of 50.11 years. Hand-grip strength was found to be lower in patients with type 2 DM than in age-matched controls. Shambhuvani *et al.* [36] assessed the effect of long-standing DM type 2 on hand-grip strength in 25 patients with diabetes since more than 6 years, who were of a mean age of 60.96 years. Grip strength was significantly reduced in diabetic individuals as compared with nondiabetic individuals.

Several studies have suggested that type 2 DM is associated with the development of frailty in the elderly [37,38]. Studies also suggest that persons aged 55 years or older should be screened for frailty [39,40].

García-Esquinas *et al.* [41] assessed the role of diabetes as a risk factor for frailty. The study included 1750 individuals (346 diabetic individuals) aged 60 years or older. The study participants were followed up to assess incident frailty. The study showed that over a mean follow-up of 3.5 years, 115 cases of incident frailty were ascertained. After adjustment for age, sex, and education, participants with diabetes showed an increased risk for frailty. They concluded that DM was associated with higher risk for frailty; this association was partly explained by unhealthy behaviors and obesity and, to a greater extent, by poor glucose control and altered serum lipid profile among diabetic individuals. Conversely, nutritional therapy to counter diabetes reduced the risk for frailty.

Also, Bouillon *et al.* [42] examined whether established diabetes risk factors were associated with future frailty in a prospective cohort study that included 2707 participants (72% men) aged 45–69 years. In that study, after a mean follow-up of 10.5 years 2.8% of the sample was classified as frail and 37.5% as prefrail. Increased age, being female, smoking, poor glycemic control, low physical activity, and not having a daily consumption of fruits and vegetables were each associated with frailty or prefrailty.

Table 2 Comparison between the studied groups regarding frailty score index

Parameters	Group I	Group II			Group III		
Frail score	*n* (%)	*n* (%)	Significance (*P*)	*t*	*n* (%)	Significance (*P*)	*t*
Nonfrail (0)	17 (85)	0 (0)	0.231	1.213	0 (0)	<0.001	13.40
Prefrail (1–2)	3 (15)	4 (16)			3 (12)		
Frail (3–5)	0 (0)	21 (84)			22 (88)		
Total	20 (100)	25 (100)			25 (100)		

Table 3 Correlations of frailty index scores in groups II and III with the duration of diabetes and the degree of diabetic control

Variables	Frail index score	
	Group II	Group III
Duration of diabetes (years)		
Pearson's correlation	0.813**	0.856**
P	<0.001	<0.001
FBS (mg/dl)		
Pearson's correlation	0.849**	0.604**
P	<0.001	<0.001
2 h pp (mg/dl)		
Pearson's correlation	0.819**	0.916**
P	<0.001	<0.001
HBA1c (%)		
Pearson's correlation	0.857**	0.847**
P	<0.001	<0.001

FBS, fasting blood glucose; HBA1c, glycated hemoglobin; *Correlation is significant at the 0.05 level (two tailed); **Correlation is significant at the 0.001 level (two tailed); 2h pp, two hours postprandial.

Low-grade chronic inflammation and impaired immune response have been noted as important factors that increase patient susceptibility to multiple chronic disease states including diabetes. In addition, increased inflammation is associated with lower muscle mass and strength and increased functional decline [43]. Thus, DM as a chronic disease associated with a chronic state of low-grade inflammation is associated with frailty.

Conclusion

Frailty is a common and growing multidimensional health and social care challenge across the world. Diabetes and frailty are causally related and operate through each of the key components of the frailty phenotype or through associated medical comorbidities. The presence of frailty in a setting of diabetes increases the level of disability and leads to poorer clinical outcomes. Diabetes is associated with frailty at earlier age. The duration of diabetes and degree of glycemic control correlate with the severity of frailty.

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Conflicts of interest

There are no conflicts of interest.

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