Combined effect of diabetes and frailty on mortality and incident disability in older Japanese adults

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Introduction

Data from the International Diabetes Federation show that the number of adults with diabetes has been gradually increasing worldwide since the 2000s, and that the number of adults with diabetes aged 65–79 years will almost double, from 98 million in 2017 to 191 million in 2045. Accordingly, strategies to prevent diabetes-related mortality and disability are required in order to prolong the healthy life expectancy of people with diabetes.

The risk of frailty has recently been acknowledged as a factor affecting the prognosis of older adults with diabetes. Older diabetes patients with frailty had more hospitalizations than did robust diabetes patients in a Chinese hospital, and a 3.6-fold tendency for the incidence of disability, as compared with non-frail participants without diabetes. These clinical and epidemiological studies, however, did not examine the combined effect of diabetes and frailty on death or disability, as compared with non-diabetic adults. Additionally, no studies have reported how frailty affects the association between diabetes and adverse outcomes in a population in Asia, which, like other regions, has an increasing diabetes prevalence. As compared with Western countries, Asian countries have a similar or even higher prevalence of diabetes, despite lower rates of overweight and obesity.

The aim of the present prospective, community-based study was to investigate the relative risks of death and disability in older Japanese adults with diabetes, frailty, both or neither at the population level.

Methods

Study cohort

The study cohort comprised 1524 residents aged ≥65 years who participated in annual health checkups carried out between 2002 and 2011 in Kusatsu, a town in Gunma Prefecture, Japan. Almost all older residents who participated in annual preventive health checkups underwent a comprehensive geriatric assessment. Participants with pre-existing disabilities (n = 71) and those with missing data (n = 182) were excluded. The data for the remaining 1271 participants (544 men and 727 women) were analyzed in the present study. Written informed consent was obtained from all participants after they were provided with a detailed explanation of the study protocol, which was approved by the ethics committee of the Tokyo Metropolitan Institute of Gerontology.

Measurement of baseline variables

The study protocol was previously described in detail. Briefly, blood was drawn from an arm, regardless of fasting status, and immediately centrifuged to separate the serum. Total cholesterol, albumin, glucose, creatinine, hemoglobin and hemoglobin A1c (HbA1c) were measured with standard methods. Estimated glomerular filtration rate was calculated by using the standardized

| Aim: Evidence is limited on how frailty affects the association between diabetes and adverse outcomes at the population level. The present community-based study aimed to clarify the relative risks of death and disability in older Japanese adults with diabetes, frailty, both or neither. |
| Methods: The present prospective study analyzed data from 1271 Japanese residents aged ≥65 years in Kusatsu town in Gunma Prefecture, Japan, who participated in annual health checkups carried out between 2002 and 2011, and were initially free of disability. A Cox proportional hazards regression model was used to identify associations of diabetes and frailty with all-cause mortality and incident disability. |
| Results: Among the 1271 participants, 176 (14%) had diabetes (mean hemoglobin A1c 7.5%, body mass index 24.2 kg/m², 45% using diabetes medications) and 151 (12%) had frailty at baseline. Compared with non-frail participants without diabetes, those with diabetes and frailty had higher risks of mortality (multivariable hazard ratio 5.0, 95% CI 2.4–10.3) and incident disability (hazard ratio 3.9, 95% CI 2.1–7.3). In contrast, non-frail participants with diabetes did not have a significantly increased risk of mortality, although they had a higher tendency for the incidence of disability, as compared with non-frail participants without diabetes. |
| Conclusions: At the population level, the risks of death and disability in persons with mild diabetes were strongly affected by the presence of frailty. From a community-based perspective, diabetes-related mortality and disability incidence might be reduced by preventing or improving frailty in conjunction with glycemic control. |
A Cox proportional hazards regression model was used to examine age- and sex-adjusted cumulative survival and disability-free rates; differences among non-frail, prefrail and frail persons were stratified by diabetes status. Hazard ratios (HR) and 95% confidence intervals (CI) for all-cause death and incident disability were calculated for prefrail and frail groups, and the non-frail group was used as reference. Person-years were calculated as the sum of individual follow-up durations until the occurrence of death or disability, or emigration from the community, whichever occurred first. To reduce the effect of reverse causality, we calculated cumulative survival, disability-free rates and HR for all-cause mortality or disability for 1214 participants, after excluding those with a follow-up period <1 year.

We adjusted for age and sex in the initial model for calculating HR, and further adjusted for other potential confounding variables, namely hypertension (systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg or antihypertensive medication use), high total cholesterol (≥5.69 mmol/L or use of cholesterol-lowering medication), low total cholesterol (<4.65 mmol/L), low estimated glomerular filtration rate (<60 mL/min/1.73 m^2), overweight (BMI ≥25.0 kg/m^2), low BMI (BMI ≤20.0 kg/m^2), anemia (hemoglobin <13.0 g/dL in men and <12.0 g/dL in women), hypoalbuminemia (serum albumin ≤3.8 g/dL), low Mini-Mental State Examination score (<23), history of stroke and current smoking. We assessed effect modification by the presence of diabetes by using an interaction term generated by multiplying the ordinal values for each frailty category (i.e. non-frail = 1, prefrail = 2, frail = 3) by diabetes status (absence = 0, presence = 1). Probability values for statistical tests were two-tailed. A P-value of <0.05 was considered to show statistical significance. All analyses were carried out with IBM SPSS Statistics version 25 (IBM Corporation, Armonk, NY, USA).

**Results**

Among the 1271 participants, 176 (14%) had diabetes (mean HbA1c 7.5%, BMI 24.2 kg/m^2, 45% used medications for diabetes), and 151 (12%) had frailty at baseline. Among participants using antidiabetic medications, 10% were insulin users. Frail participants with and without diabetes were more likely to be older and female (Table 1). Furthermore, frailty was positively associated with the use of antihypertensive medication, low total cholesterol, low Mini-Mental State Examination, history of stroke in participants without diabetes and hypoalbuminemia in those with diabetes. Mean HbA1c was 7.4–7.6% and mean BMI was 24.0–24.5 kg/m^2 in participants with diabetes, and approximately 5.5% and 23.0 kg/m^2, respectively, in those without diabetes, regardless of degree of frailty.

During follow up, we identified 275 deaths, 372 disabilities and 475 deaths or disabilities, including 172 persons who died after the disability occurred. Cumulative survival and disability-free rates worsened greatly as frailty level increased in participants without diabetes (Fig. 1). In the diabetic group, the downward trend was similar but stronger in frail participants. In non-diabetic participants, the risks of each adverse event, after multivariable adjustment, were 1.6- and approximately 2.0-fold higher in prefrail and frail participants, respectively (Table 2). Among diabetic participants, the risks of all-cause mortality and disability were also higher in frail persons. A significant interaction between the presence of diabetes and frailty category was noted for incident disability, but not for mortality.

Compared with non-frail participants without diabetes, diabetic participants with frailty had higher risks of mortality (multivariable HR 5.0, 95% CI 2.4–10.3), incident disability (multivariable HR 3.9, 95% CI 2.1–7.9) and mortality or incident disability (multivariable HR 4.1, 95% CI 2.4–7.2; Fig. 2). Non-frail participants with diabetes did not have a significantly increased risk of mortality (multivariable HR 1.1, 95% CI 0.5–2.2), although...
they had a higher tendency for the incidence of disability (multi-variable HR 1.8, 95% CI 1.0–3.2).

### Discussion

The present follow-up study of 1271 community-dwelling elderly Japanese over a mean of 8.1 years showed that the relative risks of all-cause mortality and incident disability were significantly higher (by 5.0- and 3.9-fold, respectively) in frail diabetic participants than in non-frail participants without diabetes. In contrast, the risk of mortality in non-frail diabetic participants was similar to those in non-frail participants without diabetes, although the risk of incidence of disability was 1.8-fold higher in non-frail diabetic participants compared with those having neither diabetes nor any components of frailty.

To our knowledge, this is the first study to show the combined effect of diabetes and frailty on the incidence of death and disability at the population level. A previous follow-up study of the effect of diabetes and frailty on outcomes for 1288 older Italians reported that the risk of all-cause mortality increased with greater frailty in both diabetic and non-diabetic participants. In addition, a follow-up study of 1825 older Spaniards showed a positive correlation of frailty severity with risks of all-cause mortality and...
disability in diabetic patients. These studies, however, did not report relative risks of death or disability in frail persons with diabetes compared with those without diabetes. In the present study, diabetes patients had a mean HbA1c of 7.5%, the mean BMI was 24.2 kg/m² and 45% used antidiabetic medications. The latter two values are lower than those in studies carried out in other countries, which reported a mean BMI among diabetes patients of 27.6–31.1 kg/m² and that 67–96% used antidiabetic medications.4–6,18,19 This suggests that most of the present diabetes patients had mild diabetes. The present data therefore show that, at the population level, the risks of mortality and disability in individuals with mild diabetes are strongly affected by the presence of frailty. A large-scale prospective study of approximately 350 000 UK adults aged 40–70 years reported a risk ratio of 2.79 for all-cause mortality in diabetes patients with low grip strength and 1.36 in diabetes patients with high grip strength, as compared with non-diabetic participants with high grip strength.18 Another follow-up study of 3641 Japanese community residents reported that among participants aged >65 years, the risk of all-cause mortality was significantly (4.2-fold) higher for lean participants with diabetes than for participants without diabetes who had normal BMI; however, the risk was not significantly higher in participants with diabetes who had normal BMI.20 These findings support the present results.

The present study also showed positive associations of all-cause mortality and disability with frailty in participants without diabetes, a finding consistent with those of previous population-based studies. Although it is difficult to compare risk ratios between previous studies because of variation in the definitions used for frailty, previous studies reported that frailty increased the risk of all-cause mortality by 1.2- to 2.2-fold15,16,21,22 and the risk of disability by 1.8- to 3.2-fold,15,16,22,23 as shown by multivariable-adjusted risk ratios that included diabetes as an adjustment factor.

A limitation of the present study was that the number of persons with diabetes was small, because the study population was limited to individuals who had undergone health checkups in the local community. This limitation increased the confidence intervals of risk ratios for each outcome in the analysis of frailty severity in diabetic participants. In Japan, most patients receiving treatment for diabetes do not undergo community-based health checkups, because they visit their primary care physicians. Therefore, the effect of diabetes on outcomes in the present study might be underestimated. A larger epidemiological study would yield a more accurate risk ratio for each outcome and for the interaction between diabetes and frailty. A second limitation was the small number of deaths, which made it impossible to analyze the data in relation to cause of death. Finally, we could not adequately adjust for some confounding factors associated with outcomes, including geriatric syndromes,24 such as sarcopenia;25 falls and fractures;26 diabetic complications;27 duration of diabetes;28 and socioeconomic status.29

Despite these limitations, the present study has several strengths. The comprehensive assessment, including metabolic risk factors and geriatric factors, enabled multivariate adjustment for a wide range of potential confounding variables. Additionally, complete long-term follow up for death and disability, using national vital statistics and the mandatory long-term care...
insurance system, enhances the reliability of the present findings. Furthermore, we measured serum glucose and HbA1c for all participants. These data provide an objective ascertainment of diabetes status and allow for a more robust interpretation of how diabetes severity relates to the present findings. In previous population-based studies, diabetes was ascertained by self-reported diagnosis by a physician or pharmacological treatment.5,6,18

The present findings show that preventing or improving frailty might be beneficial, in conjunction with glycemic control, for extending healthy life expectancy in persons with diabetes. Dietary and exercise interventions should be developed for different levels of frailty in diabetic persons. Although weight control is basically a preventive measure for diabetes, restrictive diets might lead to worsening anemia, hypoalbuminemia and frailty. Various dietary options should be explored for diabetic persons according to the degree of frailty. Furthermore, the present study has practical implications for frailty assessment of older adults at community-based health checkups, regardless of diabetes status. When frailty is suspected, the underlying disease should be identified and managed in a clinical setting, and a multifactorial intervention comprising resistance exercise, protein-rich food intake and a psychosocial program should be used to improve frailty.30

In conclusion, the present prospective study of Japanese older adults shows that the risks of death and disability in individuals with mild diabetes are strongly affected by the presence of frailty. The risks of all-cause mortality and incident disability among frail adults with diabetes were 5.0- and 3.9-fold, respectively, those of non-frail adults without diabetes. Non-frail participants with diabetes did not have a significantly increased risk of mortality, although they had a higher tendency for the incidence of disability, as compared with non-frail participants without diabetes. From a community-based perspective, diabetes-related mortality and incident disability might be reduced by preventing or improving frailty in conjunction with glycemic control.

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Disclosure statement

The authors declare no conflict of interest.

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