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Low glycated hemoglobin level is associated with severity of frailty in Japanese elderly diabetes patients

Ikumi Yanagita[1,2], Yuya Fujihara[1], Terumi Eda[1], Misuzu Tajima[1], Kazue Yonemura[1], Tomoko Kawajiri[1], Noriko Yamaguchi[1], Hideko Asakawa[1], Yukiko Nei[1], Yumi Kayashima[1], Mihoko Yoshimoto[1], Yuichi Kitajima[1], Mayumi Harada[1], Yuhei Araki[1], Syoji Yoshimoto[1], Eiji Aida[1], Toshihiko Yanase[2]*, Hajime Nawata[1]*, Kazuo Muta[1]

[1]Muta Hospital, and [2]Department of Endocrinology and Diabetes Mellitus, Faculty of Medicine, Fukuoka University, Fukuoka, Japan

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***Correspondence**
Hajime Nawata
Tel.: +81-92-865-2211
Fax: +81-92-865-5556
E-mail address:
h-nawata@seiwakai-muta-hp.or.jp

Toshihiko Yanase
Tel.: +81-92-801-1011
Fax: +81-92-865-5163
E-mail address:
tyanase@fukuoka-u.ac.jp

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ABSTRACT

Aims/Introduction: Previously, a study using a narrowly defined (physical base) frailty scale reported that both good and bad (U-shaped curve) glycated hemoglobin (HbA1c) levels were frailty risk factors in patients with type 2 diabetes mellitus. However, no such studies in Japan have shown this. We aimed to evaluate the frailty risk factors including HbA1c in elderly Japanese patients with type 2 diabetes mellitus using a broadly defined (both physical and psychosocial base) frailty scale, the Clinical Frailty Scale (CFS).

Materials and Methods: We randomly enrolled 132 elderly patients with type 2 diabetes mellitus (aged ≥65 years) and categorized the patients into nine stages of frailty using CFS. Because no patient had CFS 9, patients with a CFS score of 1–4 and 5–8 were defined as non-frail and frail, respectively. We attempted to identify the risk factors of frailty by investigating the association between CFS stage and various patient factors.

Results: Multiple regression analysis showed that an increase in age, low levels of albumin, high-density lipoprotein cholesterol, systolic blood pressure, HbA1c, total cholesterol, and bodyweight were statistically significant and strong independent risk factors for frailty, suggesting that reverse metabolism owing to malnutrition in elderly type 2 diabetes mellitus patients might be involved.

Conclusions: HbA1c level was not a U-shaped risk for frailty, suggesting that relatively good glycemic control might be more important for frailty than poor control in elderly type 2 diabetes mellitus patients.

INTRODUCTION

The proportion of elderly people in the population of Japan is rapidly increasing. Accordingly, the number of elderly patients (aged ≥65 years) with diabetes mellitus is increasing, and currently, ≥40% of all diabetes patients are elderly. Frailty is a state of vulnerability with poor resolution of homeostasis after stress, and is a consequence of cumulative decline in multiple physiological systems over a lifespan[1]. It is strongly linked to adverse outcomes, including falls, disability, hospitalization, care home admission and mortality[1–4]. Thus, frailty in elderly people has become an important worldwide concern[1,5].

Mounting evidence suggests that type 2 diabetes mellitus is associated with increased risk of frailty[6–8]. It is notable that elderly people with diabetes are relatively younger than those without diabetes, despite having the same frailty status. Frailty might be reversible, and people might be able to return from frailty to a condition of health with appropriate intervention. Therefore, it is important to pay attention to frailty in elderly diabetes patients and to intervene when required[9]. Such efforts help reduce the need for nursing care in elderly diabetes patients.

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Frailty has been defined in two ways. In 2001, Fried *et al.*[1] proposed their landmark frailty phenotype definition, which assessed frailty in the narrow sense by measuring physical components. After this, Rockwood *et al.*[10] and Mitnitski *et al.*[11] proposed an accumulated deficits model with a broader definition of frailty based on a comprehensive geriatric assessment, which considered not only the physical aspects, but also the psychosocial aspects of frailty. These more broadly defined models of frailty are used for setting goals of diabetes medications in Europe and America[12–15]. At Muta Hospital, Fukuoka, Japan, we use a broadly defined scale, the Clinical Frailty Scale (CFS), which has been verified as a useful rapid assessment tool of frailty[16,17] and an adverse outcome predictor.[18] The CFS is scored on a scale from 1 (very fit) to 9 (terminally ill) based on clinical judgment[19]. An increase in the category number of the scale significantly increases the risk of death.

Currently, there is little comprehensive data on the risk factors related to the degree of frailty in elderly patients with type 2 diabetes mellitus. Thus, the present study aimed to clarify the risk factors affecting the severity of frailty in elderly type 2 diabetes mellitus patients by using CFS.

METHODS

Participants

All 132 participants (63 men and 69 women) were Japanese elderly patients, aged ≥65 years. They were selected randomly and under treatment for type 2 diabetes mellitus at Muta Hospital. The diagnosis of type 2 diabetes mellitus was based on the criteria proposed by the Japan Diabetes Society[20], or had a medical history and/or medications of insulin or oral hypoglycemic agents (OHAs). The data for age, duration of diabetes, blood tests, general physical measurements and drugs were obtained from the medical records. The duration of diabetes was estimated from the initial history of hyperglycemia. In addition, follow-up data were obtained 6 months after the first examination. No intervention was made during these 6 months.

Frailty evaluation

The CFS was originally developed by Rockwood *et al.*[19], and was modified by the same group. The information is available at: http://geriatricresearch.medicine.dal.ca/clinical_frailty_scale.htm. CFS contains nine stages (1 very fit, 2 well, 3 managing well, 4 vulnerable, 5 mildly frail, 6 moderately frail, 7 severely frail, 8 very severely frail and 9 terminally ill). CFS 1–4 was defined as no frailty, because patients could live independently, whereas CFS 5–9 was defined as frailty, because patients required daily life assistance.

Hematological test and general physical measurement

The blood samples were obtained at no fixed time. We referenced the results of HbA1c, red blood cells, hemoglobin (Hb), serum albumin (Alb), aspartate aminotransferase, alanine aminotransferase, creatinine, uric acid, total cholesterol (T-chol), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol, triglyceride and corrected calcium. The estimated glomerular filtration ratio was calculated using the serum creatinine concentration. Non HDL-C was calculated by the value of T-chol minus HDL-C. We referenced the measurement results of height, bodyweight and body mass index (BMI). BMI was calculated as weight in kilograms divided by squared height in meters (kg/m^2). Systolic (SBP) and diastolic blood pressure were measured using a mercury sphygmomanometer at rest in the sitting position.

Treatments for type 2 diabetes mellitus

Participants at the time of the frailty evaluation were divided into three categories according to type 2 diabetes mellitus treatment: (i) the insulin therapy group; (ii) the OHA using sulfonylurea (SU) or glinide group; and (iii) the 'others' group. The 'others' group was treated with diet only and/or OHAs other than SU or glinide. Thus, the insulin therapy and the SU or glinide groups were considered to be relatively higher risk groups for hypoglycemia than the 'others' group. In addition, we investigated antihypertensive drugs and drugs for dyslipidemia, such as statins and fibrates.

Informed consent

The institutional review board of Muta Hospital approved the present study (date of approval: 27 June 2016, approval number: 28-001). The present study was also registered in UMIN (ID: UMIN000026203). We obtained informed consent based on the Helsinki Declaration, as revised in 2000, by publishing the opt-out to the homepage of Muta Hospital.

Statistical analysis

We defined the CFS as an objective variable. We defined the explanatory variables as the results of the hematological test, the general physical measurements, the duration of diabetes, the type of treatment and age. Comparisons between the two variable types were carried out by unpaired Student's *t*-test for mean values, and χ^2 statistic for frequencies. Multiple sample comparisons of mean values were made with the analysis of variance or Dunnett's test. Analysis with simple correlation was carried out to examine the relationships between CFS and the explanatory variables using Spearman's correlation coefficient analyses. Multiple regression analysis was carried out to identify factors independently affecting CFS using the stepwise selection method.

We compared the data of significant risk factors in multiple regression analysis with the data after 6 months. The comparisons were carried out by Wilcoxon signed rank test for the median of CFS, and the paired Student's *t*-test for the others. Data are shown as mean ± SD or *n* (%). Statistical analyses were carried out using Spss version 12.0 (SPSS Inc., Chicago, Illinois, USA), and a P-value <0.05 was considered significant.

RESULTS

Clinical characteristics of the patients

Table 1 shows the overall clinical characteristics for the 132 patients, and the clinical characteristics for the group with no frailty (CFS 1–4) and the group with frailty (CFS 5–8). As there were no patients with CFS 9, all patients were categorized into CFS 1–8. The mean levels of age, HbA1c and BMI were 78.3 ± 8.0 years, 7.1 ± 1.0% and 23.0 ± 4.4 kg/m^2, respectively. The mean values of the peripheral blood cell data including Hb, serum calcium level, liver function, kidney function, lipid levels and blood pressure showed no obvious abnormalities. In the group with frailty, the mean age was significantly higher, and mean values of HbA1c, red blood cells, Hb, Alb, HDL-C, bodyweight and SBP were significantly lower than those in the non-frailty group. The mean level of diabetes duration showed no statistical difference between the group with no frailty (CFS 1–4) and the group with frailty (CFS 5–8; Table 1).

We categorized patients according to type 2 diabetes mellitus treatments, which consisted of 19 cases with insulin therapy, 44 cases with SU or glinide and 69 cases with others. There were no significant differences in the type and number of type 2 diabetes mellitus medications between the frailty and non-frailty groups as shown by χ^2 statistics (Table 1). There was a statistically significant difference in the frequency of usage for dyslipidemia between the non-frailty group and frailty group ($P < 0.05$), but such statistical difference between the two groups was not observed in antihypertensive drugs (Table 1).

Figure 1 shows a bar graph indicating the data of each factor stratified by CFS. We defined the values in the CFS 1 group as a control, and evaluated the values in each of the CFS 2–8

Table 1 | Clinical characteristics of 132 participants and comparison of various values between the non-frailty group and the frailty group

Variable	Overall	Non-frailty CFS: 1–4	Frailty CFS: 5–8	*P*
n	132	77	55	
Age (years)	78.30 ± 7.98	75.17 ± 6.20	82.78 ± 8.16	<0.001
Duration of type 2 diabetes mellitus (years)	17.66 ± 11.31	16.89 ± 9.83	18.80 ± 13.14	NS
HbA1c (%)	7.13 ± 0.99	7.27 ± 1.04	6.60 ± 0.93	<0.001
RBC($\times 10^{12}$/L)	4.19 ± 0.64	4.38 ± 0.57	3.91 ± 0.63	<0.001
Hb (g/L)	126.34 ± 18.56	132.38 ± 17.02	117.89 ± 17.28	<0.001
Alb (g/L)	39.18 ± 5.01	41.73 ± 3.31	35.62 ± 4.82	<0.001
AST (IU/L)	23.08 ± 9.32	22.71 ± 7.16	23.58 ± 11.76	NS
ALT (IU/L)	19.36 ± 11.78	20.29 ± 10.75	18.07 ± 13.08	NS
Cre (μmol/L)	81.33 ± 43.32	80.44 ± 48.62	82.21 ± 36.24	NS
eGFR(mL/min/1.73 m^2)	63.12 ± 26.18	65.16 ± 22.11	60.26 ± 30.98	NS
UA (μmol/L)	297.40 ± 89.22	295.62 ± 71.38	299.78 ± 107.06	NS
T-chol (mmol/L)	4.63 ± 1.09	4.78 ± 1.07	4.43 ± 1.10	NS
HDL-C (mmol/L)	1.36 ± 0.42	1.46 ± 0.43	1.23 ± 0.39	<0.01
TG (mmol/L)	3.28 ± 1.68	3.30 ± 1.69	3.25 ± 1.68	NS
LDL-C (mmol/L)	2.63 ± 0.88	2.69 ± 0.88	2.54 ± 0.89	NS
Non-HDL-C (mmol/L)	3.27 ± 0.99	3.26 ± 1.08	3.21 ± 1.03	NS
Ca (mmol/L)	2.35 ± 0.12	2.32±0.10	2.35 ± 0.12	NS
Bodyweight (kg)	57.01 ± 11.99	59.17 ± 10.94	51.64 ± 12.72	<0.001
BMI (kg/m^2)	22.96 ± 4.43	23.47 ± 3.41	22.28 ± 5.49	NS
SBP (kPa)	17.26 ± 2.04	17.60 ± 1.92	16.81 ± 2.12	<0.05
DBP (kPa)	9.11 ± 1.40	9.15 ± 1.15	8.85 ± 1.67	NS
Medication for hypertension	85 (64.39)	51 (66.23)	34 (61.82)	NS
Medication with statin or fibrate	61 (46.21)	42 (54.54)	19 (34.54)	<0.05
Medications for type 2 diabetes mellitus				
Insulin	19 (14.39)	9 (11.68)	10 (18.18)	NS
Sulfonylurea or glinide	44 (33.33)	32 (41.56)	12 (21.82)	
Others	69 (52.27)	36 (46.75)	33 (60.00)	

Data are means ± SD. Data of medication of hypertension, medication with statin or fibrate and medications for type 2 diabetes mellitus are shown as *n* (%). *P*-values were determined by unpaired *t*-test. The χ^2 statistic was used to examine the frequency of the medications. Values were statistically significant at $P < 0.05$. Non-frailty group $n = 77$, frailty group $n = 55$. Alb, albumin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; Ca, calcium; CFS, Clinical Frailty Scale; Cre, creatinine; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; Hb, hemoglobin; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; NS, not significant; RBC, red blood cells; SBP, systolic blood pressure; T-chol, total cholesterol; TG, triglyceride; UA, uric acid.

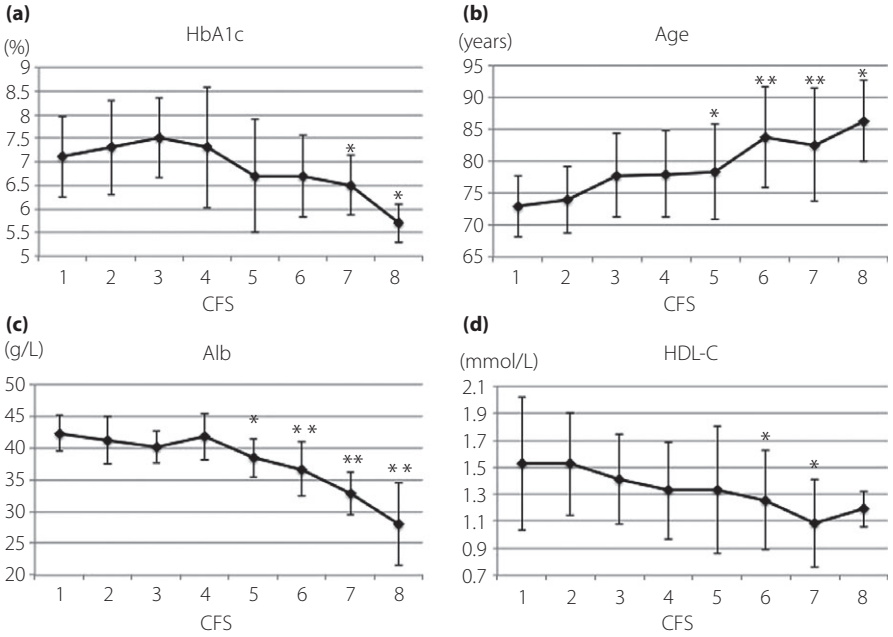

Figure 1 | Relationship between the Clinical Frailty Scale (CFS) score and values of glycated hemoglobin (HbA1c), age, albumin and high-density lipoprotein cholesterol (HDL-C). The longitudinal bars indicate the values of (a) HbA1c, (b) age, (c) albumin (Alb) and (d) HDL-C, respectively. The horizontal bar in each figure indicates the CFS score. Statistical significance was carried out using Dunnett's test. *$P < 0.05$, **$P < 0.001$.

groups using Dunnett's multiple comparisons. The values of HbA1c, Alb and HDL-C reciprocally declined with an increase in CFS. We observed these significant reductions in the CFS 7 and 8 groups with HbA1c, in the CFS 5–8 groups with Alb, and in the CFS 6 and 7 groups with HDL-C. Age increased with an increase in CFS, and the values were significant in the CFS 5–8 groups.

Analysis with simple correlation of clinical data and CFS

With simple correlation analysis, CFS values showed a significant and positive correlation with age ($r = 0.51$, $P < 0.001$). It also showed significant and inverse correlations with Alb ($r = –0.62$, $P < 0.001$), Hb ($r = –0.5$, $P < 0.001$), red blood cells ($r = –0.47$, $P < 0.001$), bodyweight ($r = –0.36$, $P < 0.001$), HDL-C ($r = –0.34$, $P < 0.001$), HbA1c ($r = –0.31$, $P < 0.01$), BMI ($r = –0.21$, $P < 0.05$) and SBP ($r = –0.2$, $P < 0.05$). CFS values did not show significant correlations with duration of diabetes, liver or kidney function, T-chol, triglyceride, low-density lipoprotein cholesterol, non HDL-C, uric acid, calcium, diastolic blood pressure and medications (Table 2).

Table 2 | Analysis of simple correlation between Clinical Frailty Scale and various values

Variable	*r*	*P*
Alb	–0.62	<0.001
Age	0.51	<0.001
Hb	–0.50	<0.001
RBC	–0.47	<0.001
Bodyweight	–0.36	<0.001
HDL-C	–0.34	<0.001
HbA1c	–0.31	<0.01
BMI	–0.21	<0.05
SBP	–0.20	<0.05
T-chol	–0.15	NS
ALT	–0.19	NS

Measurements were carried out by Spearman's correlation coefficient analyses. *r*, correlation coefficient values were statistically significant at $P < 0.05$. Alb, albumin; ALT, alanine aminotransferase; BMI, body mass index; Hb, hemoglobin; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; NS, not significant; RBC, red blood cells; SBP, systolic blood pressure; T-chol, total cholesterol.

Risk factors of frailty identified by stepwise multivariate correlation analysis

We carried out multiple regression analysis using a factor that showed a significant or nearly significant difference as an explanatory variable in a single regression analysis with the objective variable, CFS. As a result Alb ($P < 0.001$), age ($P < 0.001$), HDL-C ($P < 0.01$), SBP ($P < 0.01$), HbA1c ($P < 0.01$), T-chol ($P < 0.05$) and bodyweight ($P < 0.05$) were regarded as strong risk factors (Table 3), with Alb and age the strongest. As Hb was not a significant factor in multiple regression analysis, we found that HbA1c was a risk factor for frailty, independent of Hb.

Table 3 | Analysis with stepwise multivariate correlation between Clinical Frailty Scale and various values

Variable	β	SE	*t*-value	*P*
Alb	−1.612	0.320	−5.03	<0.001
Age	0.074	0.019	3.816	<0.001
HDL-C	−0.034	0.010	−3.538	<0.01
SBP	−0.024	0.010	−2.681	<0.01
HbA1c	−0.367	0.139	−2.639	<0.01
T-chol	−0.009	0.004	−2.421	<0.05
Bodyweight	−0.264	0.013	−2.019	<0.05

$R^2 = 0.57$. Values were statistically significant at $P < 0.05$. β, standard regression coefficient; Alb, albumin; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; SBP, systolic blood pressure; SE, standard error; T-chol, total cholesterol.

Comparing the data of CFS, HbA1c, Alb, HDL-C, SBP, bodyweight, and T-chol before and after 6 months, only the CFS value was significantly increased. HbA1c and bodyweight were significantly decreased, and Alb, HDL-C, SBP and T-chol were unchanged. The frequency in the use of hypoglycemic drugs and others was statistically not different before and after 6 months (Table 4).

DISCUSSION

The present study clarified that older age and low values of HbA1c, Alb, HDL-C, SBP, bodyweight and T-chol were independent risk factors for frailty in elderly type 2 diabetes mellitus patients. To our knowledge, this is the first report investigating the real situation of frailty in elderly type 2 diabetes mellitus patients in Japan. Our research is also unique in that the relationship between frailty and HbA1c level was analyzed using the broadly defined frailty scale, CFS.

Table 4 | Comparison of the values before and after 6 months

Variable	Previous	After 6 months	*P*
n	132	132	
CFS	3.92 ± 2.18	4.19 ± 2.18	<0.001
HbA1c (%)	7.13 ± 0.99	6.89 ± 0.91	<0.01
Bodyweight (kg)	57.01 ± 11.99	55.88 ± 11.85	<0.01
HDL-C (mmol/L)	1.36 ± 0.42	1.30 ± 0.43	NS
T-chol (mmol/L)	4.63 ± 1.09	4.49 ± 1.12	NS
Alb (g/L)	39.18 ± 5.01	38.68 ± 5.34	NS
SBP (kPa)	17.26 ± 2.04	17.07 ± 2.08	NS
Diabetes medications			
Insulin, sulfonylurea, glinide	63 (47.73)	59 (44.70)	NS
Others	69 (52.27)	73 (55.30)	NS

Data are expressed as means ± SD. Data of diabetes medications are shown *n* (%). The comparisons were carried out by Wilcoxon signed rank test for the median of CFS, and the paired Student's *t*-test for the others. Values were statistically significant at $P < 0.05$. Alb, albumin; CFS, Clinical Frailty Scale; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; NS, not significant; SBP, systolic blood pressure; T-chol, total cholesterol.

The United Kingdom Prospective Diabetes Study, which excluded people older than the age of 65 years, showed that intensive glycemic control reduced microvascular complications[21]. The Kumamoto study also reported similar data targeting Japanese type 2 diabetes mellitus patients with a mean age of approximately 50 years[22]. Then, these studies showed that the lower HbA1c, the better outcome in the control of microvascular complications. However, the Action to Control Cardiovascular Risk in Diabetes and the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation trials, which included older people, were unable to confirm that tight glycemic control reduces all-cause mortality[23,24].

Along with the effect of older age in patients with diabetes, a U-shaped risk regarding HbA1c levels was reported; not only high, but also low HbA1c levels were associated with dementia[25], stroke[26] and increased mortality[27,28]. In addition, these studies[23–28] have often discussed hypoglycemia and/or the type of medication in type 2 diabetes mellitus patients as an important contributing factor to the aforementioned incidences. However, the U-shaped association between mortality and HbA1c levels has also been reported even in non-diabetic adults[29], suggesting that low HbA1c itself might be a risk factor for increased mortality, independent of diabetic treatment and/or hypoglycemia.

As for frailty and glucose metabolism, studies have also suggested that high blood glucose is more associated with increasing the risk of frailty than low blood glucose[6,7]. In a recent report, a U-shaped relationship between glucose and frailty as evaluated by a narrowly defined frailty scale, glucose levels <8.8 mmol/L and >10 mmol/L, was associated with an increased risk of frailty, with the lowest risk at glucose levels of approximately 9.4 mmol/L[30]. To our knowledge, that study[30] is the first report showing the association of low HbA1c with frailty in elderly type 2 diabetes mellitus patients using a narrowly defined frailty scale. The report by Pilotto *et al.*[15] showed that severe hypoglycemia, as well as hyperglycemia, is related to frailty as measured with the multiple prognostic index, a kind of broadly defined scale of frailty based on a comprehensive geriatric assessment.

One possible reason for the subtle difference between the results of the present study and the previous reports[6,7,30] might be the kind of frailty scale used in the respective studies, a narrowly defined (physical based) scale, such as Fried's measurement[1], or a broadly defined (physical and psychosocial based) scale, such as the CFS or multiple prognostic index. In Japan, there have been no reports to date investigating the relationship between frailty and HbA1c levels in elderly type 2 diabetes mellitus patients. However, there are several reports regarding other events, such as the association of higher HbA1c levels with increased risk of retinopathy[31] and microangiopathy[32], and U-shaped relationships between HbA1c and stroke[26].

The reciprocal decrease of HbA1c levels with the increase of CFS stage seems to be unrelated to Hb levels, as levels of Hb were not a significant contributing factor for CFS values, as shown by multiple regression analysis. Although we could not evaluate the state or frequency of hypoglycemic attacks in participants, the number of medicines that might cause severe hypoglycemia attack (insulin, SU and glinide) was statistically not different between the non-frailty and frailty groups. Interestingly, despite the slight, but significant, improvement of HbA1c level after 6 months, CFS values were significantly worse, suggesting again that HbA1c might be a reciprocal indicator of aggravation of frailty in elderly type 2 diabetes mellitus patients.

The risk factors in middle age might change from unfavorable to favorable for survival outcome at a certain age. In other words, the risk factors of metabolic syndrome, such as high blood glucose, obesity, high cholesterol and hypertension, in middle age might shift from an unfavorable risk to favorable factors in old age. Such a contradictory shift has been called a metabolic shift and reverse metabolism[33,34]. In a study of older people (aged ≥85 years), the traditional risk factors, such as hypertension, high cholesterol and high blood glucose, did not predict risk of cardiovascular mortality[35]. Furthermore, in the study of 331 very old patients hospitalized in geriatric wards (mean age 85 ± 7 years), low BMI, low diastolic blood pressure, low T-chol and HDL-C predicted total mortality[34]. Another study reported that Alb levels and frailty had an inverse relationship in older people[36]. This is reasonable considering that hypoalbuminemia is the result of the combined effects of inflammation and inadequate protein and caloric intake in patients with chronic disease[37]. Malnutrition is closely associated not only with frailty, but also sarcopenia[38]. Because the CFS 5–8 definition[19] contains the characteristics of sarcopenia, we feel that patients in our frailty group (CFS 5–8) might also be sarcopenic depending on the severity of frailty. An explanation of the paradoxical relationship between HbA1c levels and mortality might include the 'reverse metabolic syndrome' that is probably attributable to malnutrition and/or chronic disorders[39].

In the present retrospective observational study, insulin or OHAs, such as SU and glinide, were used in 63 cases among the total 132 cases. The Japan Diabetes Society/Japan Geriatrics Society Joint Committee published a consensus statement regarding the glycemic targets of elderly patients with diabetes[40]. In this statement, a lower limit of the glycemic target was proposed to ensure safer glycemic control in those who are likely to be at risk of severe hypoglycemia. The consensus should be kept in mind not only with regard to hypoglycemic risk, but also susceptibility to severe frailty by low HbA1c levels.

In conclusion, we suggest that the risk factors of a broadly defined frailty as estimated by CFS are increase in age, low values of Alb, HDL-C, SBP, HbA1c, T-chol and bodyweight in Japanese elderly type 2 diabetes mellitus patients. In addition, a relatively lower, not higher, HbA1c level is a risk factor for frailty, independent of anemia. Further longitudinal research studies and studies using alternative frailty scales are required.

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DISCLOSURE

The authors declare no conflict of interest.

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