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Original Article

Insulin use interferes with the effect of rehabilitation in Japanese stroke patients with diabetes mellitus: A propensity score-matched analysis

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ABSTRACT

Background: The effect of using insulin on the functional outcome in patients with stroke is not well established. This study aimed to examine the effects of using insulin on Functional Independence Measure (FIM) in stroke patients with type 2 diabetes in convalescent wards.

Methods: We selected 733 stroke patients with diabetes who were discharged from Tsurumaki Onsen Hospital and Sagami Rehabilitation Hospital between April 2012 and July 2014. Among them, 169 patients had type 2 diabetes and were included in this study. In the present study, stroke patients with type 2 diabetes were divided into two groups: insulin (–) group vs insulin (+) group. We used the propensity score method to mitigate the influence of the nonrandom selection of the insulin (+) group and insulin (–) group.

Results: There were no significant differences between the insulin (–) group and the insulin (+) group with regard to background data, laboratory data (except HbA1c on discharge), and FIM score on admission and discharge among propensity-matched cohorts. However, HbA1c on discharge in the insulin (+) group after matching was significantly higher than that in the insulin (–) group. FIM gain in the insulin (+) group was significantly lower than that in the insulin (–) group after matching.

Conclusions: We revealed that it was difficult to obtain FIM gain, an indicator of ADL, at rehabilitation in stroke patients with type 2 diabetes who were insulin users compared to those who were not.

INTRODUCTION

The Ministry of Health, Labour and Welfare reports that the number of diabetic patients has increased by 460,000 from 2011 to 2014, reaching a record amount of more than 3.16 million.[1] According to the Overview of the National Health and Nutrition Survey Results in 2014, a report released by the Ministry of Health, Labour and Welfare, the rate of "people who strongly suspected diabetes" has increased rapidly in those aged 50 and upward in both sexes.[2]

In general, elderly patients with diabetes have lived with the disease for a long period of time; thus, their pancreatic β cells have, almost certainly, been totally exhausted. Additionally, there is a high possibility that insulin resistance increased in these patients because of a decrease in muscle mass associated with aging. However, because a comprehensive medicine system has been introduced in the convalescent rehabilitation ward, it is difficult to track whether insulin resistance-specific examination of patients has been conducted. Furthermore, it has been reported that insulin therapy is an independent risk factor for the decline of Activities of Daily Living (ADL).[3-4] Therefore, it is necessary to fully consider such factors in the rehabilitation of insulin-treated stroke patients. However, there are very few reports concerning rehabilitation in insulin-treated patients following stroke events. Therefore, we investigated the effects of using insulin on Functional Independence Measure (FIM) [total (T), motor (M), and cognition (C) items] in stroke patients with type 2 diabetes who were discharged from the convalescent rehabilitation ward.

METHODS

Patients

Overall, 733 stroke patients were discharged from Tsurumaki Onsen Hospital and Sagami Rehabilitation Hospital between April 2012 and July 2014. Among them,

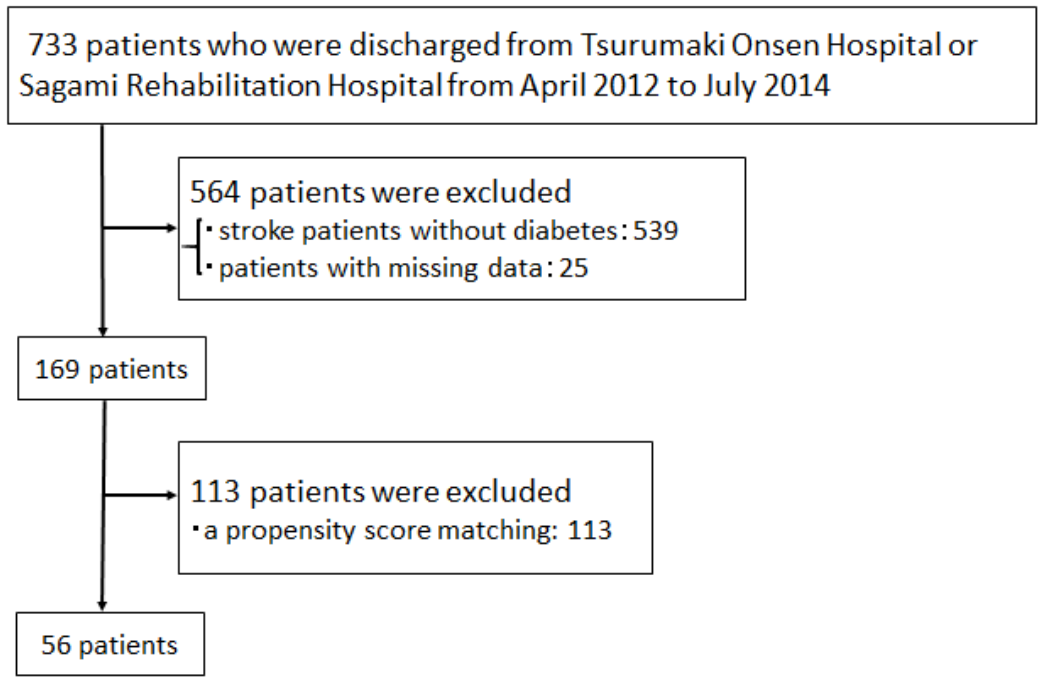

Figure 1. Flow Chart of the Trial Selection Process

169 patients had type 2 diabetes and were included in this study (Fig. 1). In the present study, stroke patients with type 2 diabetes were divided into two groups: those who did not use insulin [insulin (–) group] versus those who used insulin to control their diabetes [insulin (+) group].

The following items were recorded for both the insulin (–) and insulin (+) groups: patient background details, including sex, age, body weight (BW), length of stay, days from stroke onset to admission, medical history (e.g., Parkinson's disease, hypertension, epilepsy, dyslipidemia), and stroke subtype (cerebral hemorrhage, cerebral infarction, subarachnoid hemorrhage); antidiabetic medications taken [e.g., sulfonylurea (SU), glinide, dipeptidyl peptidase-4 inhibitor (DPP-4), α-glucosidase inhibitor (α-GI), thiazolidine, biguanide]; laboratory data, including the levels of serum creatinine (Scr), estimated glomerular filtration rate (eGFR), aspartate aminotransferase (AST), alanine aminotransferase (ALT), C-reactive protein (CRP), white blood cell (WBC), albumin (Alb), total cholesterol (T-Cho), and glycosylated hemoglobin (HbA1c); FIM score on admission and discharge (T, M, and C items); and FIM gain.

Indicators of ADL such as FIM and the Barthel index are used for evaluation during the recovery period.[5] In particular, the reliability of FIM has been confirmed in a meta-analysis of 11 studies.[6] Therefore, we used FIM to evaluate ADL in this study. FIM is a scale that assesses disability in terms of five items associated with cognition and 13 items associated with motor function in daily life, with each item scored from 1 (requiring maximum assistance) to 7 (full independence)[7] (Fig. 2). Thus, the highest total score is 126 and the lowest is 18, with higher scores indicating greater autonomy. We collected data on FIM at admission and discharge and paired this with patients' background details and laboratory data at admission. Each patient has their own professional therapists. In Japan, although the personal therapist evaluates the patient, a multidisciplinary rehabilitation team, including a rehabilitation physician, experienced nurses, physical therapist, occupational therapist, speech-language-hearing therapist, and a pharmacist determined the patient's FIM score in conferences to consult the opinions of from each specialist. In addition, experienced therapists proactively follow up unskilled therapists so that there is calibration in assessments between therapists. We calculated FIM gain scores for each patient by subtracting their FIM score on admission from their FIM score at discharge. During the observation period, certain drugs, such as some generic drugs, were changed for drugs of the same type. Otherwise, there were no other changes to patient care. The same units

FIM	Item	Content	Score
FIM Motor	Self-care	1) Eating	1–7
		2) Grooming	1–7
		3) Bathing	1–7
		4) Dressing upper body	1–7
		5) Dressing lower body	1–7
		6) Toileting	1–7
	Sphincter control	7) Bladder management	1–7
		8) Bowel management	1–7
	Transfer	9) Bed, chair, wheelchair	1–7
		10) Toilet	1–7
		11) Tub, shower	1–7
	Locomotion	12) Walk, wheelchair	1–7
		13) Stairs	1–7
FIM Cognitive	Communication	14) Comprehension	1–7
		15) Expression	1–7
	Social cognition	16) Social interaction	1–7
		17) Problem solving	1–7
		18) Memory	1–7

FIM scoring system	Score	Description
No helper required	7	Complete independence
	6	Modified independence (patient requires the use of a device but no physical assistance)
Helper (modified dependence)	5	Supervision or setup
	4	Minimal contact assistance (patient can perform 75% or more of the task)
	3	Moderate assistance (patient can perform 50%-74% of the task)
Helper (complete dependence)	2	Maximal assistance (patient can perform < 25% of the task)
	1	Total assistance (patient can perform <25% of the task or requires >1person to assist)

Figure 2. Components of functional independence measure (FIM) and its subdomain (motor and cognitive)
The FIM is one of the most common measurements of ADLs and includes 13 lower-order items regarding motor function and five lower-order items regarding cognitive function. Each item is given 1–7 points (total assistance to complete independence). The FIM total score ranges from 18 to 126 points.

of rehabilitation were performed for all patients regardless of their FIM score, severity of stroke, or length of stay at Tsurumaki Onsen Hospital and Sagami Rehabilitation Hospital.

A verbal informed consent was obtained from all participating adults.

Statistical Analysis

We compared the background details and laboratory data between patients in the insulin (–) group and those in the insulin (+) group. The results are presented as mean ± standard deviation (SD) or median (interquartile range).

We used the propensity score method to mitigate the influence of nonrandom selection in the insulin (–) and the insulin (+) groups. The propensity score[8] for an individual was defined as the conditional probability of the presence of insulin use given the individual's covariates. To estimate these scores, we created a logistic regression model on the following covariates: (I) demographic variables, such as age, sex, FIM-T, FIM-M, and FIM-C[9] at admission and (II) clinical variables, such as albumin (Alb)[10] and HbA1c levels at admission. We performed a one-to-one nearest neighbor match on the logit of the propensity score with a caliper value of 0.2. The caliper, i.e., the maximum distance between the estimated propensity scores of treated and untreated observations to be matched is generally defined as x = 0.2 of the standard deviation of the (caliper) = logit of the estimated propensity score. Percent bias calculations and t-tests were applied to check the balance of covariates both before and after matching. Balance was indicated by no apparent significance following t-tests for equality of means and a standardized bias of less than 5% after matching. Paired *t*-test, sign-rank test, and McNemar test were used where appropriate for propensity-score matched data, and statistical significance was defined as $p < 0.05$. All statistical analyses were performed using JMP Pro® (Version 12, SAS Institute Inc., Cary, NC, USA).

Ethics Regulation

This study was conducted with the approval of the Tsurumaki Onsen Hospital and Sagami Rehabilitation Hospital ethics committee. In addition, this study was conducted with the approval of the School of Pharmacy, Nihon University Ethics Committee. This was a retrospective study using medical records, which complied with the Declaration of Helsinki and the "Ethical Guidelines for Clinical Research."

RESULTS

Selection of Subjects

Figure 1 shows a flow chart of the selection of subjects. A total of 733 patients were discharged from Tsurumaki Onsen Hospital and Sagami Rehabilitation Hospital between April 2012 and July 2014. Of these, 539 did not present with diabetes mellitus, and data were missing for a further 25. We also excluded 113 patients for matching based on propensity scores. We finally selected the remaining 56 patients for this study, comprising 28 in the insulin (–) group and 28 in the insulin (+) group.

Patients' background variables before and after propensity score matching

Patients' background data for the unadjusted and propensity score-matched patients are given in Table 1. As a result, there were no significant differences between the groups with regard to all variables in both unadjusted and propensity score-matched data.

Table 1. Patients' background data by group among unadjusted and propensity-matched cohorts

Characteristic (Unit)	Unadjusted data (n = 169)			Propensity score matched data (n = 56)		
	insulin (—) (n = 118)	insulin (+) (n = 51)	*p* value	insulin (—) (n = 28)	insulin (+) (n = 28)	*p* value
Sex *n*, (%)						
Male	68 (57.6)	34 (66.7)	0.2701	13 (46.4)	18 (64.3)	0.1789
Age (years)	72 (63–80)	77 (70–81)	0.0670	71.2 ± 11.9	74.0 ± 11.0	0.3672
Weight (kg)	56.8 ± 11.3	52.2 ± 7.9	0.0775	57.1 ± 9.9	52.6 ± 8.4	0.2070
Length of stay (d)	131.5 (71.5–170)	143.0 (94–178)	0.0631	161 (132.3–177)	144 (96.5–175.8)	0.2615
Days from stroke onset to admission (d)	38 (18.5–55)	32 (16–48)	0.2477	44 (21.3–56.8)	32 (17–47.5)	0.1869
Medical history *n*, (%)						
Parkinson's disease	2 (1.7)	1 (2.0)	0.9044	1 (3.75)	1 (3.75)	1.0000
Hypertension	94 (80.0)	34 (66.7)	0.0705	24 (85.7)	19 (67.9)	0.1135
Epilepsy	11 (9.3)	6 (11.8)	0.6280	3 (10.7)	4 (14.3)	0.6862
Dyslipidemia	46 (39.0)	14 (27.5)	0.1504	8 (28.6)	6 (21.4)	0.5371
Stroke subtype *n*, (%)						
Cerebral hemorrhage	24 (20.3)	11 (21.6)	0.8563	11 (39.3)	8 (28.6)	0.3972
Cerebral infarction	87 (73.7)	36 (70.6)	0.6737	15 (53.6)	16 (57.1)	0.7881
Subarachnoid hemorrhage	7 (5.9)	4 (7.8)	0.6439	2 (7.1)	4 (14.3)	0.3875

Values are mean ± standard deviation or median (interquartile range) where appropriate.

Table 2. Antidiabetic drugs by group among unadjusted and propensity-matched cohorts

Characteristic	Unadjusted data (n = 169)			Propensity score matched data (n = 56)		
	insulin (—) (n = 118)	insulin (+) (n = 51)	*p* value	insulin (—) (n = 28)	insulin (+) (n = 28)	*p* value
Antidiabetic drugs *n*, (%)						
Sulfonylurea	34 (28.8)	14 (27.5)	0.8569	7 (25.0)	9 (32.1)	0.5541
Glinide	2 (1.79)	2 (3.9)	0.3821	0 (0)	1 (3.6)	0.3130
DPP4 inhibitor	77 (65.3)	26 (51.0)	0.0808	23 (82.1)	17 (60.7)	0.0759
α-GI	27 (22.9)	17 (33.3)	0.1552	6 (21.4)	11 (39.3)	0.1462
Thiazolidine	6 (5.1)	1 (2.0)	0.3495	3 (10.7)	1 (3.6)	0.2994
Biguanide	21 (17.8)	3 (5.9)	0.0417*	5 (17.9)	2 (7.1)	0.2254

Abbreviations: Dipeptidyl peptidase-4 inhibitor; DPP4 inhibitor, Alpha-glucosidase inhibitor; α-GI.

Table 3. Clinical laboratory data by group among unadjusted and propensity-matched cohorts

Characteristic (Unit)	Unadjusted data (n = 169)			Propensity score matched data (n = 56)		
	insulin (—) (n = 118)	insulin (+) (n = 51)	*p* value	insulin (—) (n = 28)	insulin (+) (n = 28)	*p* value
Scr (mg/dL)	0.68 (0.5–1.0)	0.65 (0.5–1.1)	0.8964	0.6 (0.5–0.7)	0.6 (0.5–1.0)	0.1736
eGFR (mL/min/1.73 m^2)	71.5 (51.1–94.2)	91.4 (52.6–98.3)	0.1200	84.8 (66.1–101.0)	93.0 (60.1–99.9)	0.8827
AST (IU/L)	23.5 (18.0–29.8)	24.0 (19.0–31.0)	0.7629	21.0 (17.3–33.3)	23.5 (19–30.5)	0.7892
ALT (IU/L)	21.0 (14.8–34.5)	23.0 (15.0–41.0)	0.6534	25.5 (16.8–38.5)	23.5 (16.3–40.3)	0.9149
CRP (mg/dL)	0.39 (0.12–1.30)	0.80 (0.21–2.81)	0.0427*	0.54 (0.2–1.4)	0.70 (0.3–2.5)	0.4630
WBC (×10^3/μL)	6.3 (5.3–8.0)	7.2 (5.3–9.2)	0.2300	7.3 ± 2.8	7.4 ± 2.4	0.9543
Alb (g/dL)	3.8 ± 0.5	3.3 ± 0.4	<.0001*	3.5 ± 0.5	3.3 ± 0.4	0.1825
T-Cho (mg/dL)	173.2 ± 39.4	154.8 ± 39.0	0.0595	179.2 ± 39.2	171.4 ± 43.7	0.6094
HbA1c at admission (NGSP) (%)	6.7 (6.1–7.4)	7.3 (6.8–8.2)	<.0001*	7.2 ± 0.8	7.2 ± 0.8	0.9492
HbA1c at discharge (NGSP) (%)	6.0 (5.7–6.4)	6.4 (6.1–6.9)	0.0004*	5.8 ± 1.2	6.5 ± 0.7	0.0132*

Values are mean ± standard deviation or median (interquartile range) where appropriate.

Antidiabetic medications data before and after propensity score matching

Antidiabetic medications data for the unadjusted and propensity score-matched patient data are given in Table 2. Biguanide users were 17.8% and 5.9% in the insulin (–) group and the insulin (+) group, respectively, with a significantly higher before matching in the insulin (–) group. After matching, there were no significant differences between the groups with regard to all medications in propensity score-matched data.

Clinical laboratory data before and after propensity score matching

Clinical laboratory data for the unadjusted and propensity score-matched patients are given in Table 3. CRP in the insulin (+) group was significantly higher than that in the insulin (–) group before matching. Similarly, HbA1c on admission and discharge in the insulin (+) group were significantly higher than those in the insulin (–) group. Additionally, Alb in the insulin (+) group was significantly lower than that in the insulin (–) group. HbA1c on discharge in the insulin (+) group was significantly higher than that in the insulin (–) group after matching. Conversely, all of the items, except HbA1c on discharge, showed no significant differences between the two groups on discharge.

FIM Score before and after propensity score matching

FIM scores for the unadjusted and propensity score-matched patients are given in Table 4. FIM on admission and discharge in the insulin (+) group were significantly lower than those in the insulin (–) group before matching. FIM gain in the insulin (+) group was significantly lower than that in the insulin (–) group after matching. On the other hand, all of the items, except FIM gain, showed no significant differences between the two groups.

DISCUSSION

The most important finding of the present study was that insulin users have the potential to interfere with the rehabilitation outcome in stroke patients with type 2 diabetes. Historically, there have been few reports affecting declining ADL in stroke patients with diabetes, but older age, peripheral neuropathy, stroke history, albuminuria, and arthritis are known as risk factors.[3-4] Furthermore, the improvement of rehabilitation in stroke patients in the presence or absence of insulin remained unreported. We investigated the effects of using insulin on FIM score in stroke patients with diabetes who were discharged from convalescent rehabilitation wards.

FIM-M gain in the insulin (+) group was significantly lower than that in the insulin (–) group. This finding may be associated with sarcopenia. In other words, lean body mass

Table 4. FIM Score by group among unadjusted and propensity-matched cohorts

Characteristic (Unit)	Unadjusted data (n = 169)			Propensity score matched data (n = 56)		
	insulin (—) (n = 118)	insulin (+) (n = 51)	*p* value	insulin (—) (n = 28)	insulin (+) (n = 28)	*p* value
FIM on admission (points)						
FIM-T	66.5 (45.5–92.5)	26.0 (19.0–69.0)	<.0001*	34.5 (28.0–43.8)	25.5 (18.3–44.8)	0.0877
FIM-M	43.5 (26.0–65.0)	17.0 (13.0–50.0)	<.0001*	20.0 (16.0–27.8)	14.5 (13.0–27.5)	0.1190
FIM-C	23.5 (14.0–31.0)	11.0 (6.0–22.0)	<.0001*	13.0 (7.8–18.0)	10.5 (5.0–19.8)	0.3656
FIM on discharge (points)						
FIM-T	103.0 (67.8–114.3)	46.0 (28.0–96.0)	<.0001*	62.0 (43.0–86.0)	39.5 (26.3–85.3)	0.0961
FIM-M	73.5 (45.0–83.0)	36.0 (18.0–72.0)	<.0001*	42.0 (32.0–63.5)	30.5 (15.3–68.0)	0.1707
FIM-C	29.0 (20.0–33.3)	17.0 (9.0–24.0)	<.0001*	18.5 (16.0–28.3)	13.0 (8.3–22.0)	0.0685
FIM gain (points)						
FIM-T	19.5 (8.8–36.3)	15.0 (4.0–27.0)	0.1231	30.5 (10.3–48.5)	14.5 (4.5–26.5)	0.0118*
FIM-M	15.0 (6.0–28.0)	11.0 (1.0–23.0)	0.0822	22.5 (8.3–41.3)	11.5 (2.0–23.8)	0.0321*
FIM-C	3.0 (0–7.0)	2.0 (0–5.0)	0.8754	6.0 (3.0–11.5)	3.0 (1.0–4.8)	0.0096*

Abbreviations: FIM-Total; FIM-T, FIM-Motor; FIM-M, FIM-Cognition; FIM-C. Values are median (interquartile range) where appropriate.

(LBM) is reduced in the elderly, which is mainly composed of skeletal muscle, which is the most important tissue targeted by insulin. Furthermore, adipose tissue increases in elderly subjects after the age of 60 years, concordant with decreasing LBM. [11] Decrease of skeletal muscle mass owing to sarcopenia leads to insulin resistance, which leads to a decrease in the mitochondrial function of the skeletal muscle with age, fat deposits in the skeletal muscle, and decreasing of autophagy.[11] In general, insulin users often have a long history of diabetic comorbidities and are more likely to exhibit poor glycemic control and greater insulin resistance. In the present study, insulin resistance details are unclear because we could not obtain the information regarding sarcopenia or laboratory data such as Homeostasis model assessment insulin resistance (HOM-R), an indicator of insulin resistance. While HbA1c in the insulin (–) group was decreased from 7.2 ± 0.8% (on admission) to 5.8 ± 1.2% (on discharge) after propensity score matching, HbA1c in the insulin (+) group was also decreased from 7.2 ± 0.8% (on admission) to 6.5 ± 0.7% (on discharge). However, the decreasing rate of HbA1c in the insulin (+) group was lower than that in the insulin (–) group. Therefore, we believe that insulin resistance was potentially relevant. Moreover, There is a possibility that numerous sarcopenia patients are present because the average age for patients within the insulin (+) group was 74 years, which means that indicating that the energy production required during exercise would have been decreased by a reduced incorporation of blood glucose into the periphery owing to the decrease of skeletal muscle. Thus, individuals in the insulin (+) group were likely to exhibit high amounts of insulin resistance. Suzuki et al. reported that stronger insulin resistance leads to a lower FIM-M gain.[12] In this study, we obtained similar results that support this finding.

FIM-C gain in the insulin (+) group was significantly lower than that in the insulin (–) group. This finding could be due to the following reasons: first, it is known that insulin has a neuroprotective role in the brain,[13] but there is a possibility that its neuroprotective action did not sufficiently benefit patients because of a hyperinsulinemic state at the periphery and in a hypoinsulinemic state in the center, arising from insulin resistance.[14] Free fatty acids released from adipose cells are increased by insulin resistance. Insulin levels in the blood increases because free fatty acids inhibit insulin-degrading enzyme. Consequently, hyperinsulinemic state in the periphery and insulin resistance are developed.[14] Second, the insulin receptor is found in high concentrations in the olfactory bulb, hypothalamus, and the hippocampus.[15-16] Therefore, the decrease in insulin action at the brain's center, due to insulin resistance may affect higher brain function. Third, when a hyperinsulinemic state presents at the periphery, an inflammatory cytokine, Tumor Necrosis Factor-α (TNF-α), increases in the cerebrospinal fluid. TNF-α inhibits the release of β-amyloid from brain to peripheral and promotes the accumulation of β-amyloid in brain. Free fatty acids released from adipose cells are increased by insulin resistance and inhibit insulin-degrading enzymes that metabolize β-amyloid. This mechanism suggests that insulin resistance is likely to be involved in the onset of Alzheimer's disease.[17-18] Thus, cognitive function may be reduced by the increase of β-amyloid due to insulin resistance. The Rotterdam study represents a large-scale epidemiological study in clinical practice, in which numerous insulin-treated patients coexisted with dementia compared with non-insulin-treated patients.[19] Therefore, we suggest that these factors can affect FIM-C gain.

Insulin resistance is improved by appropriate exercise,[20-21] and it also improves motor function[8] and maintains cognitive function.[22] Therefore, we consider that it is necessary for stroke patients with type 2 diabetes, who are able to withdraw from insulin treatment, to undergo multifaceted treatment approaches, such as combination with biguanide[23-24] or DPP-4 inhibitors that do not increase body weight. The administration of Branched-Chain Amino Acids (BCAA)[25-26] can improve muscle-building because of improved glycometabolism and further reinforce rehabilitation.

The present study contains several limitations. First, it was a cross-sectional study conducted across two centers, with only a small number of patients undergoing analysis.

Second, diabetes duration, diabetes complications such as diabetes neuropathy, and the dose of antidiabetic drug were not considered. Third, we could not analyze laboratory data using the HOMA-R, which is an index of insulin resistance. Fourth, we could not classify cerebral infarctions into subgroups, e.g., atherothrombotic infarction, lacunar cerebral infarction, or cardiogenic cerebral infarction. We believe that it is more difficult to obtain FIM gain in stroke patients than in patients with atherothrombotic infarction or lacunar cerebral infarction because cardiogenic cerebral infarction has a particularly poor prognosis among cerebral infarction. Finally, we could not analyze the Mini-Mental State Examination (MMSE) score because the amount of data was limited. However, we evaluated the cognitive function using FIM-C as a substitute for MMSE. The FIM-C score was approximately 10 points between both groups after matching. Cognitive function is not good. Thus, cognitive impairment may lead to a high risk with respect to stroke patients with diabetes in convalescent rehabilitation wards. Therefore, each of these factors could have influenced our findings. However, in the present study, there were no significant differences between the insulin (–) group and insulin (+) group in regard to FIM score at admission after matching. Therefore, the possibility of exerting an impact on our findings is low because the ADL of both groups are equivalent. However, in the future, it would be desirable to conduct a prospective cohort study in the convalescent rehabilitation ward using a sufficient sample size and laboratory data such as HOMA-R.

CONCLUSION

We observed that it is difficult to improve FIM gain, an indicator of ADL, at rehabilitation, when patients used insulin compared to those who did not. It is not sufficiently apparent whether insulin use in patients with type 2 diabetes is inevitable. Therefore, we should determine the need to assess each patient for their need of insulin and explore combination with BCAA or biguanide, which improves insulin resistance in some cases.

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The data for subjects were obtained from medical records in Tsurumaki Onsen Hospital and Sagami Rehabilitation Hospital.

CONFLICT OF INTEREST STATEMENT

The authors declare that they have no competing interests.

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