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Effects of antidiabetes drugs on functional independence measure on a subacute rehabilitation ward for stroke patients

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Received January 20, 2015, accepted February 20, 2015

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Pharmazie 70: 489–493 (2015) *doi: 10.1691/ph.2015.5523*

It has been reported that the improvement of activities of daily living (ADL) by rehabilitation affects glycemic control. However, there are no reports about antidiabetes drugs as factors affecting the outcomes of rehabilitation. Therefore, we investigated the effects of antidiabetes drugs on functional independence measure (FIM) [total (T), motor (M), and cognition (C) items] in stroke patients with diabetes who were discharged from the subacute rehabilitation ward. We chose the frequently used antidiabetes drugs [sulfonylurea (SU), dipeptidyl peptidase-IV inhibitors (DPP-IVIs), and α-glycosidase inhibitors (α-GIs)] as the basis for categorizing the patients. We compared the patients' background features and laboratory data among the three groups. As a result, when SU was used in stroke patients with diabetes, it is difficult to obtain significant FIM-M gain, FIM-C gain, FIM-M efficiency, and FIM-C efficiency compared with α-GIs. As a reason for this, we hypothesize the possibility of the involvement of insulin resistance. Therefore, we consider that insulin resistance should be determined early and that it is important to reduce insulin resistance comprehensively by involving experts.

1. Introduction

The Ministry of Health, Labour and Welfare has reported the "Outline of the 2012 National Health and Nutrition Survey Results". The number of people strongly suspected of having diabetes is approximately 9.5 million and that of people who are confirmed to have diabetes is estimated to be approximately 11 million in Japan. Of the patients who are strongly suspected of having diabetes, the percentages of males and females currently receiving treatment are 65.9% and 64.3%, respectively. The numbers of males and females with diabetes continue to increase every year. It is estimated to increase further with the super-graying of the Japanese society. In addition, diabetes is a promoting factor for arteriosclerosis, and diabetic patients are more likely to develop atherothrombotic cerebral infarction (Chukwuma et al. 1993; Currie et al. 1997). The number of patients requiring treatment in the subacute rehabilitation ward has been increasing.

The purpose of rehabilitation of diabetic patients is to maintain a complication-free healthy condition as much as possible. During rehabilitation, the patients are appropriately educated and instructed on how to minimize participation restriction and limitation of activity (Sato 2003). However, it has been reported that the effect of such a rehabilitation of stroke patients with diabetes is small because such patients show many complications during hospitalization (Golden et al. 2005). Therefore, an improvement of glycemic control has been expected in subacute rehabilitation wards. It has been reported that the improvement of activities of daily living (ADL) by rehabilitation affects glycemic control (Suzuki et al. 2005). However, there are no reports about antidiabetes drugs as factors affecting the outcomes of rehabilitation. Therefore, we investigated the effects of antidiabetes drugs on Functional Independence Measure (FIM) [total (T), motor (M), and cognition (C) items] in the stroke patients with diabetes who were discharged from the subacute rehabilitation ward.

2. Investigations and results

2.1. Patients background

The Fig. 1 shows the flow chart of the selection of subjects in this study. There were 2701 patients who were discharged from Tsurumaki Onsen Hospital within the observation period. Among them, 1068 were discharged from wards other than the subacute rehabilitation ward, 323 were hospitalized more than 60 days after the onset of the stroke, 207 showed high FIM scores at admission, and 31 had missing data. We excluded these patients from the study (total, 1629). Next, for further screening, we identified 337 patients with diseases other than cerebrovascular disease, 596 nondiabetic patients, 59 patients who used insulin, and 2 patients with missing data. We also excluded these patients from the study (total, 994). We finally selected the remaining 78 patients for this study.

2.2. Combination of drugs

Table 1 shows the combination of sulfonylurea (SU), dipeptidyl peptidase-IV inhibitors (DPP-IVIs), and α-glycosidase

Table 1: Combination of concomitant drugs

SU	Glinide	DPP-IVIs	α - GIs	Metformin	Pioglitazone	Number of concomitant drugs	n	Total
Drugs concomitantly taken with SU (monotherapy: n = 2)								
		○				1	8	13
			○				5	
		○			○	2	1	2
		○		○			1	
		○	○	○		3	1	1
Drugs concomitantly taken with DPP-IVIs (monotherapy: n = 24)								
○						1	7	21
			○				9	
				○			4	
					○		1	
○					○	2	1	3
	○		○				1	
○				○			1	
Drugs concomitantly taken with α-GIs (monotherapy: n = 14)								
○						1	4	16
		○					8	
				○			3	
					○		1	
	○	○				2	1	1
○		○		○		3	1	1

inhibitors (α-GIs). The drugs that were most frequently used in combination with SU were DPP-IVIs (11 patients, 61.1%), followed by α-GIs (6 patients, 33.3%). The monotherapy with SU was observed in 2 patients (11.1%). Next, the drugs that were most frequently used in combination with DPP-IVI were α-GIs (10 patients, 20.8%), followed by SU (9 patients, 18.8%). The monotherapy with DPP-IVI was found in 24 patients (50.0%). The drugs that were most frequently used in combination with α-GIs were DPP-IVIs (10 patients, 31.3%) followed by SU (5 patients, 15.6%). The monotherapy with α-GIs was found in 14 patients (43.8%).

2.3. Patients' background features and laboratory data of three groups on admission

Table 2 shows the patients' background features and laboratory data of the three groups. There were no significant differences in the investigated items related to the patients' background features such as sex, age, length of stay, number of days from the onset of stroke to hospitalization, and FIM score on admission among these three groups. There were no significant differences in laboratory data such as aspartate aminotransferase (AST), alanine aminotransferase (ALT), serum creatinine (Scr), and albumin (Alb) levels among the three groups. However, glycohemoglobin (HbA1c) in SU group was 7.9 ± 1.4%. It was significantly higher than other two groups.

2.4. Effect of FIM gain and FIM efficiency in the three groups

Table 3 shows the effect of FIM gain (FIM score on discharge minus FIM score on admission) and FIM efficiency (FIM gain divided by length of stay) in the three groups. The FIM-M gains in the SU and α-GI groups were 14.3 ± 10.7 and 23.9 ± 12.4, respectively, which were significantly different. Similarly, the FIM-C gain in the SU and α-GI groups were 1.9 ± 4.8 and 6.2 ± 5.6, respectively, which were also significantly different. The FIM-M efficiencies in the SU and α-GI groups were 0.13 ± 0.08 and 0.31 ± 0.24, respectively, which were significantly different. Similarly, the FIM-C efficiencies in the SU and α-GI groups were 0.03 ± 0.08 and 0.05 ± 0.11, respectively, which were significantly different. On the other hand, no significant differences in FIM-T gain and FIM-T efficiency were observed between the two groups. In addition, no significant differences in all the items of FIM gain and FIM efficiency were observed between the SU and DPP-IV groups.

3. Discussion

This study is, to the best of our knowledge, the first to clarify the effects of antidiabetes drugs on FIM. The most important finding is that when SU was used in stroke patients with diabetes, it was more difficult to obtain significant FIM-M gain, FIM-C gain, FIM-M efficiency, and FIM-C efficiency than when α-GIs were used. It has been reported that the improvement of ADL by rehabilitation affects glycemic control. However, there are no reports about the antidiabetes drugs as factors affecting the outcomes of rehabilitation. In this study, the following radically new findings were noted.

Diabetes is a risk factor for severe infection and macrovascular disorders such as cerebral infarction. The number of patients treated for diabetes has been increasing even in the subacute rehabilitation ward, and diabetes has been reported to affect the functional prognosis of rehabilitation (Air and Kissela 2007). Diabetes has three major complications (i.e. retinopathy, neuropathy, and nephropathy). It also leads to various disorders owing to the effects of aging. There are many points that should be carefully considered in the rehabilitation of stroke patients with diabetes (Kohzuki 2009). However, there are no reports about antidiabetes drugs as factors affecting the outcome of reha-

Table 2: Patients' background features and laboratory data of drug-based groups on admission

Variables	SU group (n=18)	DPP-IVI group (n=48)	α-GI group (n=32)	*p* value
Sex (male / female)	9 (50.0%) / 9 (50.0%)	28 (58.3%) / 20 (41.7%)	22 (68.8%) / 10 (31.3%)	0.3983
Age	76.0±9.2	76.4±10.3	74.7±9.2	0.6385
length of stay (days)	115.7±43.5	112.0±52.7	111.5±55.3	0.9865
number of days from onset to hospitalization (days)	26.9±18.4	23.1±18.0	21.3±15.9	0.5892
AST level (IU/L)	23.4±8.2	28.3±13.9	28.1±9.8	0.2394
ALT level (IU/L)	24.7±10.5	27.6±21.7	28.7±17.7	0.6796
Scr level (mg/dL)	0.8±0.3	0.8±0.3	0.8±0.2	0.6171
Alb level (g/dL)	3.5±0.5	3.6±0.4	3.6±0.3	0.9871
HbA1c level (%)	7.9±1.4	6.8±1.0	7.0±1.3	0.0070*
FIM-T score	60.4±23.2	56.6±25.7	63.3±26.1	0.5344
FIM-M score	41.5±21.5	38.0±19.7	44.1±18.9	0.5587
FIM-C score	20.3±10.2	19.3±14.6	20.3±8.7	0.6792

* We used the Kruskal-Wallis test and χ^2 test to compare the three groups. Significances of individual differences were evaluated by the post-hoc-test when differences in the Kruskal-Wallis test were significant. Results: SU vs DPP-IV, p =0.0058; SU vs α-GI, p =0.0363. Values are mean ± standard deviation. Abbreviations : FIM-Total (FIM-T), FIM-Motor (FIM-M), FIM-Cognition (FIM-C)

Table 3: Effects of FIM gain and FIM efficiency in drug-based groups

FIM gain	SU group (n=18)	DPP-IVI group (n=45)	α-GI group (n=31)	*p* value
FIM-T score	19.3±19.1	25.6±21.3	25.8±17.8	0.5624
FIM-M score	14.3±10.7	23.4±15.8	23.9±12.4	0.0462
FIM-C score	1.9±4.8	4.9±5.1	6.2±5.6	0.0444

FIM efficiency	SU group (n=18)	DPP-IVI group (n=45)	α-GI group (n=31)	*p* value
FIM-T score	0.15±0.29	0.28±0.32	0.27±0.29	0.3493
FIM-M score	0.13±0.08	0.27±0.24	0.31±0.24	0.0167
FIM-C score	0.03±0.08	0.01±0.27	0.05±0.11	0.0409

We used the Kruskal-Wallis test to compare the three groups. Significances of individual differences were evaluated by the post-hoc-test when differences in the Kruskal-Wallis test were significant. Values are mean ± standard deviation. Abbreviations: FIM-Total (FIM-T), FEM-Motor (FIM-M), FIM-Cognition (FIM-C)

bilitation. Therefore, in this study, we chose three types of drugs (SU, DPP-IVIs, and α-GIs) that are highly frequently used in combination in diabetic patients and examined their effects on FIM.

In this study, it was difficult to obtain significant FIM-M gain and FIM-M efficiency in the SU group compared with the α-GI group. The reason for this may be the involvement of insulin resistance, as reported previously. Suzuki et al. (2005) assessed insulin resistance using homeostasis model assessment ratio (HOMA-R). They investigated the correlation between FIM-M gain and the amount of change in HOMA-R on admission and discharge. As a result, they found that the increase in HOMA-R is large, namely, FIM-M gain tended to be low when insulin resistance is high. Therefore, we also investigat insulin resistance in this study. Ismail-Beigi (2012) reported on the expected reduction in HbA_{1c} level. According to the report, HbA_{1c} levels were decreased by 1.0-1.5% by SU and by 0.5–0.9% by α-GIs. Therefore, the degree of HbA_{1c} reduction by SU is higher than that achieved by α-GIs. However, the HbA_{1c} levels in the SU and α-GI groups on admission were 7.9 ± 1.4% and 7.0 ± 1.3%, respectively, in this study. The SU group showed a significantly higher degree of reduction than the α-GI group. We were unable to investigate HOMA-R sufficiently, which is the evaluation index of insulin resistance, similarly to Suzuki et al. (2005) because our study was a retrospective observational study. However, the patients had received the antidiabetes drugs in their previous hospitals for a long time and continue to take them currently. Therefore, as the reasons why the HbA_{1c} level in the SU group were high, we hypothesized that SU is involved in insulin resistance due to its long-term prescription in the previous hospitals of the SU group.

There is another report suggesting insulin resistance of the SU group. Tajiri et al. (2010) reported that the decrease in lower extremity muscle mass, which is commonly observed in patients with type 2 diabetes, shows a significant correlation with insulin resistance. In addition, glucose transporter (GLUT) 4, which has a major role in glucose uptake into cells, is highly expressed in muscle cells (O'Gorman et al. 2006). Therefore, when the mass

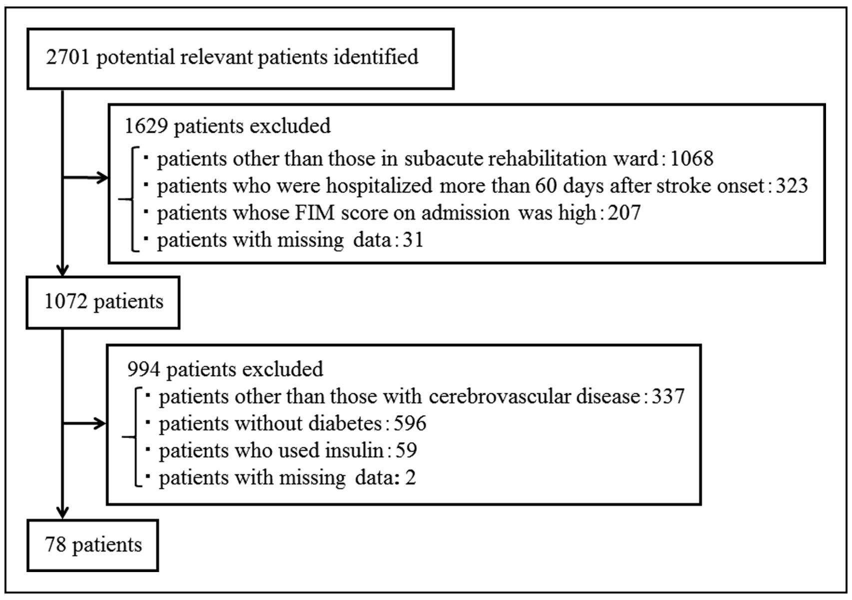

Fig. 1: Flow Chart of Trial selection Process.

of muscle decreases, the expression level of GLUT 4 should also decrease. We hypothesize that the mass of muscle affects blood glucose control or insulin resistance. That is, we considered that the blood glucose level is improved because glucose is taken up into the cells when FIM-M gain is high. In this study, we investigated the association between FIM-M gain and the improvement of HbA_{1c} levels in the SU group. As a result, there was no significant correlation between the FIM gain and the improvement of HbA_{1c} levels ($r = -0.2564$, $p = 0.4467$).

In light of these reports, we hypothesize that there are many patients with insulin resistance and decreased muscle mass in the SU group. Therefore, we consider that it is necessary for patients to do more resistance exercise, which increases muscle mass, or aerobic exercise, which improves insulin resistance and blood glucose level. Furthermore, we consider that it is necessary to recommend the uptake of branched-chain amino acid formulations (e.g., formulations containing high levels of the essential amino acid leucine or L-isoleucine), because such essential amino acids promote the synthesis of skeletal muscle protein in the elderly (Ikehara et al. 2008). L-Isoleucine promotes the uptake of glucose into the skeletal muscle and prevents the increase in blood glucose levels (Ikehara et al. 2008). In addition, we consider that insulin resistance should be detected early by measuring HOMA-R and C- peptide levels, for example, in patients treated with SU. If indicated, we should consider resistance exercise and the administration of branched-chain amino acid formulation as mentioned above. We consider that it is important to develop approaches that reduce insulin resistance comprehensively.

On the other hand, it was more difficult to obtain significantly high FIM-C gain and FIM-C efficiency in the SU group than in the α-GI group. The reason for this may be found in the following reports. Sakurai et al. (2006) observed greater brain atrophy in elderly diabetic patients than in nondiabetic patients. There also are studies showing that insulin resistance develops possibly because the neuroprotective action of insulin wanes owing to the reduced transport of insulin to the brain, reduced insulin activity in the brain, and β-amyloid accumulation in the cell (Craft 2005; Baura et al. 1996). In light of these reports, we hypothesized that there are many patients with insulin resistance in the SU group. Therefore, we considered that SU possibly affects FIM because it induces neurodegenerative disorders such as dementia *via* the reduction of the transport of insulin to the brain.

The limitations of this study are as follows. First, it is a cross-sectional study within a single facility and the number of patients studied was small. Second, we were unable to sufficiently examine the factors (e.g., severity of stroke or diabetes, history of falls, presence of hypoglycemia, duration of diabetes, the dosage of each drug, HOMA-R, and Mini-Mental State Examination (MMSE) score) associated with the effects of rehabilitation or the decrease in cognitive function, because this was a retrospective observational study. Third, we were unable to examine antidiabetes drugs other than the three because the frequency of their use was low. These limitations may have affected the results of this study. We consider that it is desirable to perform a prospective study in the future that satisfies the following conditions. First, a sufficient number of patients should be recruited and data on the presence of insulin resistance or cognitive function should be collected. Second, data on the combination of various types of antidiabetes drugs should be unified.

We revealed an association between FIM and SU. Subacute rehabilitation wards do not necessarily have diabetes specialists. Therefore, we hypothesize the possibility that antidiabetes drugs have been inaccurately prescribed. It is desirable to achieve good glycemic control in order to carry out rehabilitation safely because stroke patients with diabetes have a variety of symptoms. For this purpose, it is necessary to carry out total care by a multifaceted approach involving rehabilitation physicians, nurses, pharmacists, dietitians, and rehabilitation staff. We consider that this approach will lead to function improvement and prevent the recurrence of stroke in patients with diabetes.

4. Experimental

We chose the antidiabetic drugs frequently used in combination SU, DPP-IVIs, and α-GIs as the basis for categorizing the patients. We categorized the patients into the SU, DPP-IV, and α-GI groups. We compared the following items among the three groups.

The patients' background features examined were sex, age, length of stay at Tsurumaki Onsen Hospital, number of days from the onset of stroke to hospitalization, FIM score on admission (T, M, and C items), FIM gain, and FIM efficiency. The laboratory data examined were the levels of AST, ALT, Scr, Alb, and HbA_{1c}.

The indicators of ADL such as FIM and the Barthel index are used for evaluation during the recovery period (Saeki 2009). In particular, the reliability of FIM has been confirmed in a meta-analysis of 11 studies (Ottenbacher et al. 1996). Therefore, we used FIM to evaluate ADL in this study. FIM is an index of the ability in terms of 5 items related to cognition and 13 items related to the motor function in daily life in seven stages from the stage requiring maximum assistance (1 point) to that of full independence (7 points). FIM has a total of 18 items (5 cognitive items and 13 motor function items). The lowest score is 1 and the highest score is 7 for each item. The highest total score is 126 and the lowest is 18. The degree of autonomy also increases with the score (Heinemann et al. 1993). It has been reported that the FIM-M gain and home reversion rate become worse approximately 60 days after the onset of stroke (Yoshida and Takada 2006). In addition, it has been reported that insulin treatment is an independent risk factor for reducing ADL (Sakurai 2013). Therefore, in this study, we excluded the patients who had more than 60 days until hospitalization from the onset of stroke and those who used insulin. Furthermore, we categorized the patients into those with high (110-126 points), moderate (80-109 points), and low (18-79 points) FIM scores on admission as in a previous study (Hirata 2008). We targeted the patients with more than moderate scores. We used the data on FIM gain and FIM efficiency on admission and discharge. We also used the data on the patients' background features and laboratory data on admission. The rehabilitation team was composed of a physician, experienced nurses, and the rehabilitation staff (physical therapist, occupational therapist, and speech-language-hearing therapist) in charge of the subacute rehabilitation ward. They discussed and evaluated the patients' FIM as a team. We calculated FIM gain and FIM efficiency. Regarding the drugs used during the observation period, there were changes to generic drugs or drugs of the same type but no other changes. The same units of rehabilitation were carried out for all patients regardless of their FIM score, severity of stroke, and length of stay at Tsurumaki Onsen Hospital.

4.1. Subjects

Of the 2701 patients who were discharged from Tsurumaki Onsen Hospital from January 2011 to November 2013, 78 patients with type 2 diabetes, who did not use insulin, and who had stroke complications were recruited in this study (Fig. 1).

4.2. Statistical analysis

We compared the three groups (SU group, DPP-IV group, and α-GI group) in terms of their background features and laboratory data. The results are presented as mean ± S.D. We performed the Shapilo-Wilk W test to compare the data volume among the three groups. We used the Kruskal-Wallis test to compare the three groups. Significances of individual differences were evaluated by the post-hoc-test when differences in the Kruskal-Wallis test were significant. We used the χ^2 test to compare categorical data. The significance level was 5% ($p \leq 0.05$). Statistical analyses were performed using JMP® (Version 10, SAS Institute Inc., Cary, NC, USA).

4.3. Ethical regulation

This study was conducted with the approval of the Tsurumaki Onsen Hospital Ethics Committee. In addition, this study was conducted with the approval of the School of Pharmacy, Nihon University Ethics Committee (Approval number: 14-008). This was a retrospective study using medical records that complied with the Declaration of Helsinki and the "Ethical Guidelines for Clinical Research."

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