

# One-minute mental status examination for category fluency is more useful than mini-mental state examination to evaluate the reliability of insulin self-injection in elderly diabetic patients

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## Keywords

Elderly, Insulin, Self medication

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## ABSTRACT

**Aims/Introduction:** We investigated the factors associated with the reliability of insulin self-injection in elderly diabetic patients receiving insulin therapy.

**Materials and Methods:** We enrolled diabetic patients aged  $\geq 65$  years and receiving insulin therapy, and assessed their cognitive function by the mini-mental state examination and 1-min mental status examination for category fluency. We also observed their technique of insulin self-injection, and evaluated whether or not patients were able to inject insulin by themselves according to nine defined details in terms of insulin self-injection. The predictive factors for the reliability of insulin self-injection were determined by univariate and multivariate logistic regression analysis. There were 278 participants (135 males, 143 females) enrolled in the present study.

**Results:** According to multivariate logistic regression analysis, only the 1-min mental status examination score was found to be a significant independent predictor of the reliability of insulin self-injection (odds ratio 0.75; 95% confidence interval 0.62–0.90;  $P = 0.002$ ).

**Conclusions:** The 1-min mental status examination for category fluency can be considered more useful than mini-mental state examination to evaluate the reliability of insulin self-injection in elderly diabetic patients receiving insulin therapy.

## INTRODUCTION

Insulin therapy is the most effective treatment for glycemic control in diabetic patients, and it is indispensable for type 1 diabetes. Many diabetic patients inject insulin by themselves daily in cases of worsened glucose metabolism, and some develop diabetic ketoacidosis. Difficulties, such as physical and/or mental disabilities, render them unable to carry out insulin self-injection.

In such cases, they must be helped by family members, nurses and doctors to administer their insulin treatment.

Diabetes is associated with a significantly increased risk of cognitive decline and dementia<sup>1,2</sup>. It is easy to understand why elderly diabetic patients with dementia cannot correctly self-inject insulin, and consequently their glycemic control worsens. To the best of our knowledge, there is no report showing an association between cognitive dysfunction and insulin self-injection. The question is what degree of cognitive function is neces-

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sary for diabetic patients to correctly self-inject insulin. Also, there is the question of whether other factors are associated with the ability to self-inject insulin reliably, for instance age, glycaemic control or years of education.

Therefore, we examined the factors associated with the reliability of insulin self-injection in elderly diabetic patients receiving insulin therapy.

## MATERIALS AND METHODS

We enrolled 278 consecutive diabetic patients aged  $\geq 65$  years and receiving insulin therapy. We obtained data on patients' age, duration of diabetes and insulin therapy, age at the start of insulin therapy, average glycosylated hemoglobin (HbA1c) during the previous 3 months and total years of education.

HbA1c values were converted from Japan Diabetes Society (JDS) values to National Glycohemoglobin Standardization Program (NGSP) values using the following formula: HbA1c (NGSP equivalent value) (%) =  $1.02 \times \text{HbA1c (JDS value) (%) + 0.25\%$  (i.e., NGSP [%] = JDS [%] + 0.3% in the range of JDS  $\leq 4.9\%$ ; NGSP [%] = JDS [%] + 0.4% in the range of JDS 5.0–9.9%; and NGSP [%] = JDS [%] + 0.5% in the range of JDS 10–14.9%)<sup>3</sup>.

Patients were administered both the mini-mental state examination (MMSE)<sup>4</sup> and the 1-min mental status examination for category fluency (inquiring about the participant's name, and asking him or her to list as many different animals as possible in 1 min)<sup>5</sup> in order to evaluate their cognitive function. We also observed each patient's insulin self-injection technique. Some patients received help with self-injection from family members or caregivers. However, we assessed these patients' ability to inject insulin without such help.

Only one patient injected insulin by 1-cc syringe (Humulin N<sup>®</sup>; Eli Lilly, Indianapolis, IN, USA). All the other patients used pen-type insulin devices, such as FlexPen<sup>®</sup> (Novo Nordisk, Bagsvaerd, Denmark), MirioPen<sup>®</sup>/KwikPen<sup>®</sup> (Eli Lilly) and SoloSTAR<sup>®</sup> (Sanofi, Paris, France).

We defined the following nine points as important details when determining whether patients were able to inject insulin by themselves: (i) open the cap of the insulin device; (ii) check the amount of insulin remaining in the cartridge; (iii) attach the hypodermic needle; (iv) set up the target dial; (v) prick the skin with the needle; (vi) push the syringe plunger directly and smoothly; (vii) inject insulin for more than 5 s; (viii) recheck the dial at '0' after the injection; and (ix) remove the needle and close the cap of the insulin device. Use of sterile technique (e.g., sterilizing the injection site with an alcohol swab before injection) was not considered essential for insulin self-injection. If a patient was unable to follow any of the aforementioned instructions, we classified insulin self-injection as 'impossible' for him or her.

The current study was approved by the Research Ethics Committee of the Health Education Center Science Clinic (Yokohama, Japan), and all patients gave written informed consent before the start of the study.

## Statistical Analysis

All statistical analyses were carried out using IBM SPSS 21.0 software for Windows (Chicago, IL, USA). All results were expressed as means  $\pm$  standard deviation or numbers. Continuous variables in the two groups were compared using an unpaired Student's *t*-test or Mann–Whitney test according to the data distribution with or without normality. Categorical variables were analyzed by Fisher's exact test. The predictive factors for the reliability of insulin self-injection were assessed by univariate and multivariate logistic regression analyses. The resulting odds ratios (ORs), as well as 95% confidence intervals (CIs), are reported, along with the *P*-values.

According to the average HbA1c during the previous 3 months, we divided the patients into three groups:  $<6.9\%$  as reference, 6.9–8.3% and  $\geq 8.4\%$ . If there was collinearity between the two variables, one was excluded from the multivariate regression model. In addition, the receiver operating characteristics (ROC) curve was used to determine the cut-off value of an independent predictor factor, and to assess the accuracy for the reliability of insulin self-injection. A *P* value of  $<0.05$  was considered statistically significant.

## RESULTS

Table 1 summarizes the patients' characteristics. Table 2 shows the patients' characteristics for the 'impossible' and 'possible' groups. Data from three people were excluded because important components of their insulin injection technique could not be assessed. The mean age and average HbA1c during the previous 3 months in the 'impossible' group were significantly higher than in the 'possible' group. The mean MMSE score and 1-min mental status examination score in the 'impossible' group were significantly lower than in the 'possible' group. There was no significant difference in the mean of duration of diabetes, duration of insulin treatment, age at start of insulin treatment or total education between the two groups.

The ORs and 95% CIs for each predictive factor related to the reliability of insulin self-injection, as analyzed by univariate and multivariate logistic regression analysis, are shown in Table 3. According to multivariate logistic regression analysis, only the 1-min mental status examination score was an

**Table 1** | Patient characteristics

Male/female	135/143
Age (years)	75.3 $\pm$ 5.9
Duration of diabetes (years)	21.6 $\pm$ 10.2
Duration of insulin treatment (years)	9.58 $\pm$ 7.67
Age at start of insulin therapy (years)	65.6 $\pm$ 9.1
Average HbA1c, previous 3 months (%)	7.78 $\pm$ 1.23
Total education (years)	12.0 $\pm$ 3.5
Mini-mental status examination score	25.6 $\pm$ 3.8
1-min mental status examination score	11.8 $\pm$ 3.8

Data are expressed as numbers or means  $\pm$  standard deviation (*n* = 278). HbA1c, glycosylated hemoglobin.

**Table 2** | Patients' characteristics of the 'impossible' and 'possible' groups

	Impossible group (n = 29)	Possible group (n = 246)	P-values
Male/female	17/12	117/129	0.327*
Age (years)	78.0 ± 4.6	75.0 ± 6.0	0.010†
Duration of diabetes (years)	25.7 ± 12.5	21.1 ± 9.8	0.061†
Duration of insulin treatment (years)	9.74 ± 8.06	9.49 ± 7.55	0.874‡
Age at start of insulin therapy (years)	68.3 ± 7.5	65.4 ± 9.1	0.062†
Average HbA1c, previous 3 months (%)	8.46 ± 1.97	7.70 ± 1.10	0.002†
Total education (years)	11.2 ± 3.0	12.0 ± 3.6	0.256†
Mini-mental status examination score	22.8 ± 5.0	25.9 ± 3.5	<0.001†
1-min mental status examination score	8.7 ± 2.8	12.2 ± 3.7	<0.001†

Data are expressed as numbers or means ± standard deviation. As determined by \*Fisher's exact test, †unpaired *t*-test, ‡Mann–Whitney test. HbA1c, glycated hemoglobin.

independent factor associated with the reliability of insulin self-injection (OR 0.75; 95% CI 0.62–0.90; *P* = 0.002).

The cut-off value and the area under the curve (AUC) in the ROC curve are shown in Table 4. A 1-min mental status examination score of ≤10 predicted insulin self-injection to be 'impossible', with a sensitivity of 65.6% and a specificity of 69.0%. As this AUC was 0.77 (95% CI 0.69–0.85; *P* < 0.001), the accuracy of a cut-off 1-min mental status examination score of 10 was estimated as 77%.

## DISCUSSION

The aim of the present study was to investigate what factors are associated with the reliability of insulin self-injection in

**Table 4** | Cut-off value and the area under the curve in the receiver operating characteristics curve with 1-min mental status examination for the reliability of insulin self-injection

	Cut-off value	AUC (95%CI)	P-value
1-min mental status examination score	10	0.77 (0.69–0.85)	<0.001

AUC, area under the curve.

elderly diabetic patients receiving insulin therapy. Age, average HbA1c during the previous 3 months, MMSE score and 1-min mental status examination score were significantly different between the 'impossible' and 'possible' groups. These were also associated factors for the reliability of insulin self-injection by univariate analysis.

The glycemic target for patients with diabetes should be individualized. The position statement of the American Diabetes Association and the European Association for the Study of Diabetes states that a HbA1c of <7.5–8.0% might be acceptable, transitioning upward as age increases and capacity for self-care; cognitive, psychological and economic status; and support systems decline<sup>6</sup>. The present study suggests that HbA1c levels of ≥8.4% might not be desirable for elderly diabetic patients receiving insulin therapy regarding the reliability of insulin self-injection. Also, it might be necessary to consider the fact of poor technique of insulin self-injection causing the worsening of glycemic control to ≥8.4%.

The present study shows that cognitive dysfunction, as indicated by MMSE score and/or 1-min mental status examination for category fluency score, is associated with the reliability of insulin self-injection. A MMSE score to assess cognitive function might be an important component of the clinical evaluation of patients with type 2 diabetes mellitus<sup>7</sup>. However, the MMSE has some disadvantages, including insensitivity to the

**Table 3** | Predictors for the reliability of insulin self-injection determined by univariate and multivariate logistic regression analysis

	Univariate Odds ratio (95% CI)	P-values	Multivariate Odds ratio (95% CI)	P-values
Male	1.56 (0.72–3.41)	0.263	1.53 (0.56–4.20)	0.406
Age ≥75 years	2.95 (1.21–7.15)	0.017	1.29 (0.38–4.36)	0.686
Duration of diabetes ≥20 years	1.61 (0.72–3.60)	0.249	2.10 (0.69–6.38)	0.193
Age at start of insulin therapy ≥65 years	2.43 (1.00–5.94)	0.051	1.68 (0.51–5.52)	0.397
Average HbA1c, previous 3 months (%)				
<6.9	Reference	0.004	Reference	0.160
6.9–8.3	0.79 (0.25–2.46)	0.686	1.56 (0.36–6.70)	0.552
≥8.4	3.28 (1.12–9.65)	0.031	3.66 (0.81–16.55)	0.092
Total education <12 years	1.41 (0.58–3.42)	0.443	1.01 (0.36–3.14)	0.986
Mini-mental status examination score	0.84 (0.77–0.92)	<0.001	0.96 (0.83–1.10)	0.532
1-min mental status examination score	0.74 (0.65–0.85)	<0.001	0.75 (0.62–0.90)	0.002

HbA1c, glycated hemoglobin.

earliest changes in highly educated individuals and lack of ability to measure executive function. Yamazaki *et al.*<sup>8</sup> reported that at least 30 of 240 elderly diabetic patients in whom family and medical staff had not noticed any cognitive impairment, but who had received a diagnosis of evident dementia, including early Alzheimer's disease (AD) or mild cognitive impairment (MCI), were overlooked by the MMSE screening criteria. In addition, it is not easy to administer MMSE to numerous elderly diabetic patients at a crowded routine clinical practice for outpatients, because the examination takes 10–15 min.

Hanyu *et al.*<sup>5</sup> reported that 1-min category fluency is the best measure to discriminate patients with AD from control subjects, with 87% of AD patients correctly classified using an optimal cut-off score of 13 (sensitivity 0.91, specificity 0.81). They also concluded that 1-min category fluency is the best instrument to distinguish patients with MCI from control subjects, with 75% of MCI patients correctly classified using an optimal cut-off score of 14 (sensitivity 0.81, specificity 0.69). Therefore, Hanyu *et al.* suggested that the 1-min category fluency can be applied as a screening test in clinics.

After multivariate logistic regression analysis, the 1-min mental status examination score was shown to be the only factor independently associated with the reliability of insulin self-injection in the present study. Because it is difficult to observe and evaluate the insulin injection technique for all patients receiving insulin therapy, we might be able to use the 1-min mental status examination to select patients whose insulin self-injection technique should be checked. In this way, 1-min category fluency is useful to evaluate not only cognitive function, but also the reliability of insulin self-injection.

It is unclear why patients with cognitive dysfunction lose the ability to continue to inject insulin by themselves. Semantic category fluency test score is associated with functions of the medial temporal lobe, which includes the hippocampus and entorhinal cortex<sup>9–15</sup>. Kitabayashi *et al.*<sup>16</sup> reported that semantic category fluency is most strongly correlated with blood flow to the left posterior temporal cortex (Brodmann's areas 22–37). A functional magnetic resonance imaging system study showed that temporal lobe activation is required for the process of retrieval by category in control subjects<sup>9</sup>. Semantic category fluency requires a search through semantic or conceptual memory, and it is critically dependent on an adequate knowledge of the physical and/or functional attributes that define a particular semantic category. Accordingly, semantic category fluency has been found to rely on lateral and inferior temporal lobe regions known to be involved in object perception, recognition, imagery, and naming<sup>15–18</sup>. Episode memory, such as face recognition, word recognition and random recall, is also highly dependent on the medial temporal lobe<sup>19</sup>. Considering the results of the present study, the process of the insulin self-injection technique might be associated with the medial temporal lobe function.

The present study had some limitations. First, we selected the 1-min mental status examination for category fluency

using only the category 'animals'. We consider that the category 'animals' is more appropriate than the category 'vegetables' to measure semantic category fluency, because it is not affected by sex differences<sup>20</sup>. However, the influence of individual differences cannot be denied, because the examination was carried out using only one category. Second, we did not administer the 1-min mental status examination for letter fluency. This test is as easy as category fluency test, and has been found to correlate with prefrontal lobe functioning<sup>21</sup>. If the association between letter fluency and the reliability of insulin self-injection is established in future studies, it would be expected to contribute to the elucidation of how the action of insulin self-injection is processed in the brain.

In conclusion, the present study shows that an independent associated factor for the reliability of insulin self-injection is not the MMSE score, but rather the 1-min mental status examination score for category fluency. This examination is more useful than the MMSE to evaluate the reliability of insulin self-injection in elderly diabetic patients receiving insulin therapy.

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