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Relationship between grip strength and minimal clinically important differences in cognitive function in older adults with dementia in a long-term residential facility

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Objective. Non-pharmacological approaches effectively improve cognitive function in older adults with dementia in institutionalised settings. We aimed to investigate the physical characteristics of older adults with dementia achieving a minimal clinically important difference (MCID) on the Mini-Mental State Examination (MMSE) following interventions for cognitive rehabilitation based on exercise.
Methods. This retrospective analysis included 25 participants with dementia residing in a long-term care facility who underwent group exercise in a quasi-randomised controlled study. We calculated the MCID on the MMSE using a distribution-based method. The rounded values of the standard deviation (SD) of the MMSE at baseline of approximately 0.4 and 0.5 were considered an MCID. Based on intervention outcomes, the participants were divided into MCID achievers and non-achievers. We compared changes in physical function based on grip strength, maximum knee extension strength, maximum 10-m gait time, and 5-m wheelchair driving time.
Results. MCID achievers had significantly higher grip strength at baseline than non-achievers for both 0.4 × SD and 0.5 × SD. A multiple logistic regression analysis including age, sex, and MMSE at baseline revealed that grip strength was significantly associated with MCID achievement at 0.4 × SD (odds ratio [OR], 1.614; 95% confidence interval [CI], 1.04-2.51) and 0.5 × SD (OR, 1.585; 95% CI, 1.04-2.42).
Conclusions. The importance of measuring grip strength was demonstrated by considering the achievement of an MCID for cognitive function. Assessing objective changes using a distribution-based method may help evaluate rehabilitation outcomes. Higher grip strength at baseline was significantly associated with MCID improvement in the MMSE in institutionalised older adults with dementia.

Key words: cognitive rehabilitation, grip strength, minimal clinically important difference, Mini-Mental State Examination, physical activity

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INTRODUCTION

Many reports on non-pharmacological approaches for dementia have provided evidence supporting their effects on cognitive ability, activities of daily life (ADL), and physical functions in institutionalised settings [1,2]. Residents in long-term care facilities have low physical activity (PA) and

few opportunities for social engagement [3]; thus, there is a high risk of further functional decline [4]. It is important to provide a rehabilitation program that includes both physical and social elements to sustain patient function in an institutionalised setting [5,6]. A previous study reported that interventions with exercises affect cognitive function [7]. Possible mechanisms underlying exercise and cognitive function have been explained by locomotor [8,9] (e.g., increase in PA and prevention of falls), nervous system-related [10-12] (e.g., expression of brain-derived neurotrophic factor), and cardiovascular factors [13] (e.g., optimisation of blood pressure and lipid metabolism). Additionally, the use of group dynamics and the emphasis of mutual communication with others bring about positive effects and increase adherence to dementia rehabilitation [14-16]. Our previous studies have reported the effects of group-based physical interventions on cognitive function and quality of life (QOL) of older adults living in long-term care facilities [17,18].

The efficacy of non-pharmacological approaches, such as rehabilitation for dementia, has been demonstrated in clinical settings by observing the responses of patients to interventions, although some interventions are not necessarily effective for all patients. By understanding the characteristics of patients in whom clinically significant improvements are achieved, the selection of an individualised therapy might facilitate decision-making in dementia rehabilitation. For example, knowing these patient characteristics enables rehabilitation professionals to decide on the appropriate treatment for patients early. Furthermore, patients themselves can determine which treatment methods have effects suitable to their needs. In recent years, there has been a trend to translate the impact of clinical research from statistical significance to clinical relevance, in which a minimal clinical important difference (MCID) is a criterion for judging therapeutic effects. MCIDs have several advantages for conducting rehabilitation. First, MCID helps interpret whether treatment effects are clinically relevant. Second, although raw or basic statistical data (e.g., mean ± standard deviation [SD]) can only evaluate whether the improvement is statistically significant, MCIDs are used as a criterion to determine whether the therapeutic effect is in a clinically meaningful range. Although dementia rehabilitation has been reported to have a 'significant' effect on maintaining and improving cognitive function based on the findings of systematic reviews and meta-analyses [2,19,20], the achievement of an MCID has not been described.

MCIDs can be obtained by anchor-based and distribution-based methods [21,22]. The anchor method, relying on expert opinions or patient-based outcomes, is an established and valid method to confirm the clinical relevance of an intervention. A recent systematic review of the distribution method for dementia reported that a baseline SD of 0.4 or 0.5 was the MCID for the Mini-Mental State Examination (MMSE) score [23,24], which is believed to be clinically meaningful and useful [25].

Physical functions protect cognitive function [26-28], and grip strength is a known predictor of cognitive decline [26,29,30]. Based on the above findings, we aimed to clarify the physical functions, such as grip strength, of people who can significantly obtain improvements from intervention involving physical exercise. By clarifying the characteristics of the physical functions, it may be possible to show the physical functions necessary for maintaining or improving the cognitive functions of institutionalised patients with dementia. This study aimed to clarify the association of baseline physical function with MCID achievement in cognitive function and to examine whether relevant physical functions were associated with MCID even after considering covariates.

MATERIALS AND METHODS

Patient enrolment and interventions

We retrospectively reviewed data from a previous randomised control trial [17,18]. These trials were registered in University Hospital Medical Information Network Clinical Trial Registry (UMIN trial ID: UMIN000023083). We assessed 215 participants for eligibility, 91 of whom were allocated to the intervention or control group. After a follow-up evaluation, 28 and 24 participants were allocated to the intervention and control group, respectively. The inclusion criteria were as follows: i) presence of dementia (MMSE score, 5–25 points); ii) absence of problems associated with participating in a group activity; iii) absence of severe auditory or visual impairment; iv) ability to freely move around the facility regardless of aid, and v) admission duration of > 3 months. The intervention group received 45-60 min of group-based PA, which included reality orientation, seated exercises (stretching, self-weight muscle strength training, and aerobic exercise), and cognitive training or stimulation. The intervention was performed two times per week, and lasted 8-12 weeks. The control group received usual care. The mean adherence rate of the intervention was 88.3 ± 26.6%. Outcome measures were performed twice before and after the intervention. We confirmed significant improvement of cognitive function, maintenance of social activity, and improvement of QOL in group-based intervention. The mean difference of the MMSE score between before and after intervention was 1.72 ± 2.39 points.

Determination of the MCID for therapeutic outcomes

We calculated the MCID of the MMSE score using a distribution-based method. Based on the SD of the MMSE score at baseline, we multiplied SD by 0.4 and 0.5 and defined this rounded-off value as the MCID. Then, the participants were divided into two groups: MCID achievers and non-achievers.

Measurements

Five occupational therapists and one speech therapist independent of the intervention have assessed global cognitive functions (MMSE [24]), physical functions (grip strength, maximum knee extension strength, 10-m gait time, and 5-m wheelchair driving time), and independence of ADL (Barthel Index [31]) for each clinical trial. Measurements were performed twice before and after intervention. MMSE [24] represents global cognitive function and consists of time orientation, place orientation, immediate and delayed three-word playback, calculation, item naming, sentence repetition, three-stem oral command, written command, sentence writing, and figure copying. Assessment staff evaluated the MMSE in a private quiet environment. Grip strength was measured using Grip-D (Takei Scientific Instruments, Tokyo, Japan), and the maximum of two measurement on dominant or nonparetic side was selected as representative data. Grip strength was measured in a sitting position, with the participants using an armrest. The maximum knee extension strength was measured using μTas F-100 (ANIMA, Tokyo, Japan) in terms of isometric muscle strength with the knee joint flexed at 90°, and the maximum value of two measurements on the dominant or nonparetic leg was considered representative. The maximum knee extension muscle strength was measured with the participants being in a sitting position with both soles not touching the ground. Each participant held the armrest during the measurement. Moreover, the 10-m gait time was measured to determine the maximum gait speed. The participants walked a total of 14 m of walkway, including 2 m each of the acceleration and deceleration sections, and assessment staff measured the intermediate 10-m walking time [32]. In addition, the 5-m wheel chair driving time was measured using a stopwatch. The assessment staff measured the time for the participants to drive the wheelchair from a stationary to 5 m ahead. The Barthel Index [31] was scored based on the participants' living situation and basic movement ability.

Statistical analysis

The Shapiro-Wilk test was used to confirm the normality distribution of the MMSE score. The Mann-Whitney U test and Fisher's exact test were used to compare the two groups and to check the independence of each baseline measurement. Furthermore, a multiple logistic regression analysis was performed using the forced entry method with MCID achievement as a dependent variable, and significant items in the two-group comparison and the independence test were considered independent variables. Age, sex, adherence rate of intervention, and baseline MMSE scores were used as covariates. We employed post-hoc power analysis of the multiple logistic regression. The SPSS Statistics for Windows version 25.0 (IBM Corp., Armonk, NY, USA) was used for statistical analysis. Statistical significance was set at $p < 0.05$.

RESULTS

Patient characteristics

The median (interquartile range [IQR]) age of participants

Table I. Characteristics of overall participants.

	Intervention group		Control group	
	(N = 25)		(N = 24)	
	N	%	N	%
Sex (female, n)	16	64.0	19	79.2
Using wheel chair(n)	14	56.0	11	45.8
CDR				
0-0.5	3	12.0	3	12.5
1	13	52.0	9	37.5
2	4	16.0	5	20.8
3	5	20.0	7	29.2
	Median	IQR	Median	IQR
Age	89	84-92	87	82-91
MMSE	16	12-20	15.5	11.5-20
GDS-5	2	1-3	2	1-3
Grip strength(kgf)	14.8	11.9-16.4	12.2	9.7-14.6
Maximum knee extension strength(kgf)	11.6	8.7-14.7	11.8	9.2-14.9
Maximum 10m gait time(s)	14.0	10.4-17.5	12.9	11.4-19.5
5m w/c drive time(s)	34.5	14.0-49.0	30.2	11.4-43.3
Barthel Index	60	50-85	75	50-85

Abbreviations: CDR: Clinical Dementia Rating; MMSE: Mini-Mental State Examination; GDS: Geriatric Depression Scale-5; IQR: interquartile range; SD: standardized deviation.

Table II. MMSE scores at pre- and post-intervention and relative SDs.

	MMSE score					0.4×SDpre	0.5×SDpre
	Median	IQR	Mean	SD	P†		
Pre	16	12.20	15.72	5.02	0.389	2.01	2.51
Post	17	14.20	17.44	5.05	0.443		
Post-pre	2	-1.3	1.72	2.39	0.092		

Abbreviations: †: Shapiro-Wilk test. MMSE: Mini-Mental State Examination; IQR: Interquartile range; SD: standardized deviation.

Table III. Difference between MCID achievers and nonachievers in physical function in intervention group.

	0.4 × SD					0.5 × SD				
	noMCID (n=11)		MCID(n = 14)		P	noMCID (n = 13)		MCID (n = 12)		P
	N	%	N	%		N	%	N	%	
Sex(Female, n)	9	81.8	7	50	0.208	10	76.9	6	50	0.226
	Median	IQR	Median	IQR	P	Median	IQR	Median	IQR	P
Age	88	82.5-92	90	84.25-92.5	0.727	88	84-92	90	84.5-92	0.682
MMSE	17	15-21	14	12-18	0.187	16	14-20	13	11-20	0.229
Grip strength(kgf)	12.5	10.9-14.4	15.65	14.95-18.7	0.004	12.6	11.7-15	16.4	14.9-19.4	0.006
Maximum knee extension strength(kgf)	11.1	8.0-13.2	13.5	10-16	0.258	11.1	8.8-12.4	13.5	9.3-19.2	0.213
Maximum 10m gait time(s)	13.04	12.4-15.9	15.13	7.65-17.73	0.865	13.04	12.4-15.9	15.13	7.7-17.7	0.865
5m w/c drive time(s)	40.36	27.2-48.3	14.58	10.65-54.0	0.749	40.36	25.8-48.7	14	7.3-58.9	0.641
Barthel Index	55	47.5-70	70	55-85	0.295	55	50-75	70	55-85	0.311
Adherence rate (%)	100	93.8-100	100	100-100	0.809	100	87.5-100	100	100-100	0.538

Abbreviations: MCID: minimal clinically important difference; MMSE: Mini-Mental State Examination; IQR: interquartile range; SD: standardised deviation.

was 89 (84-92) years, and the percentage of women was 63.9%. The adherence rate to this intervention was 89.4%, and the dropout rate was 22.2%. Finally, 25 and 24 participants were divided into the intervention and control groups, respectively (Tab. I).

MCID

The median (IQR) and mean (SD) at baseline for MMSE scores were 16 (12-20) points and 15.72 (5.02) points, respectively. The Shapiro-Wilk test showed the normal distribution of the pre, post, and pre-post difference in the MMSE score. The MCID based on the distribution method was 2.01 for 0.4 × SD and 2.51 for 0.5 × SD, and the rounded off values (0.4 × SD: 2.0, 0.5 × SD: 3.0) were used for the analysis (Tab. II).

Differences in physical function between MCID achievers and non-achievers

There were significant differences in grip strengths at baseline between MCID achievers and non-achievers at both 0.4 × SD (n = 14, 11) and 0.5 × SD (n = 12, 13). There were no significant differences with respect to other items (Tab. III). Additionally, we compared the characteristics between MCID achievers and non-achievers in the control group. There was significant difference in age at baseline between MCID achievers and non-achievers at 0.4 × SD (n = 10, 14). In addition, there were no significant differences between the two groups in other items (Tab. IV).

Involvement of grip strength

A multiple logistic regression analysis revealed that grip

Table IV. Difference between MCID achievers and nonachievers in physical function in control group.

	0.4×SD					0.5×SD				
	noMCID(n = 14)		MCID(n = 10)		P	noMCID(n = 16)		MCID(n = 8)		P
	N	%	N	%		N	%	N	%	
Sex(female, n)	11	78.6	9	90.0	0.615	12	75.0	7	87.5	1.000
	Median	IQR	Median	IQR	P	Median	IQR	Median	IQR	P
Age	84	79-89.5	90	88-93	0.026	85	81-91	90	87.5-92	0.169
MMSE	15	12-21.5	15	11-18	0.373	16	12-21	15	11-17	0.152
Grip strength(kgf)	11.8	10.0-14.6	12.6	10.3-17	0.890	11.8	9.4-14.2	12.6	10.4-18.4	0.503
Maximum knee extension strength(kgf)	11.5	8.4-19.2	13.4	10.5-14.5	0.725	11.5	7.9-18.1	13.4	11.2-14.4	0.854
Maximum 10m gait time(s)	12.1	11.4-16.8	15.1	12.5-19.8	0.385	12.1	11.3-20.0	15.1	12.9-19.1	0.358
5m w/c drive time(s)	12.1	8.7-64.2	35.3	30.2-40.3	0.770	12.1	8.7-64.2	35.3	30.2-40.3	0.770
Barthel Index	70	57.5-82.5	82.5	60.0-85.0	0.450	70	65-85	82.5	50-87.5	0.791

Abbreviations: MCID: minimal clinically important difference; MMSE: Mini-Mental State Examination; IQR: interquartile range; SD: standardised deviation.

Table V. Multiple regression analysis for the achievement of MCID.

	Unadjusted			Adjusted		
	Odds	95% CI	P	Odds	95% CI	P
0.4 × SD						
Grip strength(kg)	1.273	0.98-1.65	0.066	1.614	1.04-2.51	0.036
0.5 × SD						
Grip strength(kg)	1.231	0.97-1.56	0.083	1.585	1.04-2.42	0.035

Abbreviations: Covariates: sex, age, adherence rate of the intervention, Mini-Mental State Examination scores at baseline

strength was a significant factor in achieving MCID even after considering covariates at 0.4 × SD (odds ratio [OR], 1.614; 95% confidence interval [CI], 1.04-2.51) and at 0.5 × SD (OR, 1.585; 95% CI, 1.04-2.42). The post hoc analysis showed that critical z and power(1-β) were 1.65, 0.58 at 0.4 × SD, and 1.65, 0.15 at 0.4 × SD, respectively (Tab. V).

DISCUSSION

This study aimed to clarify the physical functions associated with achieving an MCID on the MMSE score. The multiple logistic regression analysis revealed that grip strength at baseline was associated with achieving an MCID in the MMSE score at 0.4 × SD and 0.5 × SD. In contrast, there was no association between MCID achievement and physical functions in the control group. Based on this finding, the importance of measuring the grip strength was demonstrated by considering the achievement of an MCID for cognitive function.

In this study, values of 2.01 for 0.4´SD and 2.51 for 0.5´SD (by rounding off: 2.0 for 0.4´SD, 3.0 for 0.5´SD) were calculated using a distribution-based method. A previous study suggested that a change of 2-3 points in the MMSE score is clinically meaningful [33]; therefore, this result could be considered a valid value.

In general, an anchor-based method is used to define a significant MCID of clinical value. In the anchor-based method, external measures that assess concepts similar to outcomes are preferred [34], for example, subjective reports from patients or assessments by experts. However, for individuals with dementia, subjective reports on changes in cognition may be inaccurate because individuals with moderate-to-severe dementia do not necessarily have objective metacognitive ability [35]. In addition, there are few facilities with specialised professionals and few opportunities to obtain systematic evaluations. Therefore, assessing objective changes using a distribution-based method, as in this case, may be a meaningful measure to evaluate the effects of rehabilitation.

In the comparison between groups, the MCID achievers had a significantly higher grip strength at baseline than the non-achievers. Additionally, grip strength was

significantly associated with the achievement of an MCID even after adjusting for covariates.

Grip strength is related to cognitive decline in older adults [36-38], but its effects in individuals with moderate-to-severe dementia residing in institutional settings remain unclear. There are several possible mechanisms underlying this phenomenon. First, muscle strength, such as grip strength, rather than muscle mass [39], is associated with insulin-like growth factor 1 and brain-derived neurotrophic factor levels, which play important roles in improving cognitive function by promoting neuronal plasticity and neurogenesis [40]. Second, grip strength can contribute to the extent of PA, which is influenced by independence in ADL. PA protects against cognitive decline in individuals with Alzheimer's disease [7]; therefore, maintaining physical functions for institutionalised older adults is of great importance [6]. A systematic review investigating the association between PA and grip strength confirmed the relationship between total PA, moderate-to-vigorous PA, light PA, and grip strength [41]. Furthermore, several reports have shown a relationship between grip strength and ADL independence in older individuals requiring nursing care [42,43]. Therefore, grip strength, which is related to maintaining independence in daily life and activity levels, may suppress the decline in cognitive function. Furthermore, the proportion of older adults using wheelchairs as a means of daily mobility by themselves (14 of 25, 56%) might have influenced the lack of association between MCID and other physical functions.

The impaired domains of cognitive function may vary based on the baseline cognitive function [44]. For example, the main symptoms of mild dementia are presumed to involve recall and orientation in time, and those of moderate to severe dementia are presumed to involve drawing and registration. Therefore, the impact on daily living might be different depending on cognitive function. Further investigation is required to determine whether the impact of MCID on daily functioning differs depending on the baseline cognitive function.

This study had several limitations. As we did not employ an anchor-based method, there was no validated way to confirm sufficient clinical improvements. Owing to the small sample size and low power, caution should be exercised while generalising the results. Although there was no statistical association between MCID achievement and sexual difference, the sexual difference might have affected the relation between grip strength and MCID achievement. Therefore, further studies are needed to examine differences according to sex. As more than half of the participants in this study had dementia and used wheelchairs as a means of mobility in a non-institutionalised setting, these findings might not be applicable in other settings. In our previous trials, it was not possible to obtain information on educational background. Therefore, further analysis, which considers educational background on MMSE, would be needed. Additional studies are required with a larger number of participants from different settings to explore the physical functions associated with improvement of cognitive function or other outcomes.

CONCLUSIONS

This study showed the importance of evaluating grip strength as a marker of significant improvement of cognitive function in rehabilitation among individuals with dementia. These results could be useful for prognosis prediction and decision-making in rehabilitation for dementia.

Conflict of interest statement

The authors declare no conflict of interest.

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Author contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by ST; the first draft of the manuscript was written by ST, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Ethical consideration

This study was approved by the Ethics Review Board of Takasaki University of Health and Welfare (approval number: 2820) based on the Declaration of Helsinki. Written consent was obtained from each participant and their family after they were provided complete information on the purpose of the study, risks and benefits, confidentiality, anonymity, and freedom of participation.

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