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Clinical Research Article

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Effects of a Tailored Exercise Intervention in Acutely Hospitalized Oldest Old Diabetic Adults: An Ancillary Analysis

Nicolás Martínez-Velilla,[1,2] Pedro L. Valenzuela,[3] Mikel L. Sáez de Asteasu,[1,2] Fabricio Zambom-Ferraresi,[1,2] Robinson Ramírez-Vélez,[1,2] Antonio García-Hermoso,[1,2,4] Julian Librero-López,[1] Javier Gorricho,[5] Federico Esparza Pérez,[5] Alejandro Lucia,[2,6] and Mikel Izquierdo[1,2]

[1]Navarrabiomed, Complejo Hospitalario de Navarra-Universidad Pública de Navarra, Institute for Health Research of Navarre (IdiSNA), 31008, Pamplona, Spain; [2]Networking Biomedical Research Center (CIBER) of Frailty and Healthy Aging, Instituto de Salud Carlos III, 28029 Madrid, Spain; [3]Department of Systems Biology, University of Alcalá, 28805 Madrid, Spain; [4]Laboratorio de Ciencias de la Actividad Física, el Deporte y la Salud, Facultad de Ciencias Médicas, Universidad de Santiago de Chile, USACH, Santiago, Chile; [5]Department of Health, Government of Navarra, 31002 Pamplona, Spain; and [6]Faculty of Sport Sciences, Universidad Europea de Madrid and Research Institute Hospital 12 de Octubre, 28670 Madrid, Spain

ORCiD numbers: 0000-0002-1506-4272 (M. Izquierdo).

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Abstract

Objective: To analyze the effects of a tailored exercise intervention in acutely hospitalized elderly diabetic patients.
Research Design and Methods: This is an ancillary analysis of a randomized controlled trial (RCT). A total of 103 acutely hospitalized elderly adults (mean age ~87 years) with type II diabetes were randomized to an intervention (exercise, n = 54) or control group (usual care, n = 49). The primary endpoint was change in functional status from baseline to hospital discharge as assessed with the Barthel Index and the Short Physical Performance Battery (SPPB). Secondary endpoints comprised cognitive function and mood status, quality of life (QoL), incidence of delirium, and handgrip strength. Exercise-related side effects, length of hospital stay, and incidence of falls during hospitalization were also assessed, as well as transfer to nursing homes, hospital readmission, and mortality during a 3-month follow-up.
Results: The median length of stay was 8 days (interquartile range, 4) for both groups. The intervention was safe and provided significant benefits over usual care on SPPB (2.7 [95% confidence interval (CI) 1.8, 3.5]) and Barthel Index (8.5 [95% CI: 3.9, 13.1]), as well as on other secondary endpoints such as cognitive status, depression, QoL, and handgrip strength (all $P < 0.05$). No significant between-group differences were found for the remainder of secondary endpoints.

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Conclusions: An in-hospital individualized multicomponent exercise intervention was safe and effective for the prevention of functional and cognitive decline in acutely hospitalized elderly diabetic patients, although it had no influence on other endpoints assessed during hospitalization or at the 3-month follow-up after discharge.

Key Words: multicomponent physical exercise intervention, functional decline, cognitive impairment, cardiometabolic risk factors, Vivifrail

The global number of adults with diabetes mellitus (DM) has almost quadrupled in the last decade (1). The numerous complications associated with DM include cardiovascular diseases, peripheral neuropathy, retinopathy, chronic renal failure, and mental health (2, 3). In older populations, DM seems to contribute to an increased prevalence of multimorbidity, polypharmacy, and disability, which subsequently increases the risk of frailty, institutionalization, and financial burden for health care systems (4).

Particularly worrying are the consequences of DM for the elderly (ie, those aged >80 years), especially during periods of hospitalization. Older adults have an increased vulnerability to the adverse consequences of hospitalization, which frequently leads to an incomplete recovery of preadmission functional and cognitive status upon discharge (5) and, thus, to an increased risk of nursing home admission and mortality (6). In this regard, over 40% of hospitalized elderly patients with DM, which is associated with longer hospital stays, are at an increased risk of complications and overall mortality compared with their normoglycemic peers (7, 8). Thus, diabetic patients seem to be at greater risk of nosocomial disability (2, 9).

Physical exercise has been proposed as a cornerstone in the treatment of DM (10). Although there is still some reluctance to promote physical exercise among acutely hospitalized elderly adults (11), growing evidence supports the benefits of in-hospital exercise interventions in this patient population (12, 13). In a recent study, we showed that tailored, multicomponent exercise intervention prevented the functional and cognitive decline commonly observed in acutely hospitalized older adults (12, 13). Although there is rationale to support exercise interventions that might be beneficial in a vulnerable population such as old diabetic in-patients, to the best of our knowledge no study has analyzed the effects of in-hospital exercise on these individuals.

In this ancillary analysis of our previous RCT, we aimed to analyze the effects of individualized exercise interventions in acutely hospitalized elderly adults with DM.

Methods

Study design and participants

This study is a secondary analysis of a randomized controlled trial (RCT; NCT02300896) that was conducted from February 1, 2015, to August 30, 2017, in the Acute Care of the Elderly unit of the geriatrics department of a tertiary public hospital. The specific details of the study are available elsewhere (12).

Briefly, acutely hospitalized patients who met the inclusion criteria were randomly assigned to an intervention or control (usual care) group within the first 48 hours of admission. We focused on a particularly vulnerable population segment but with a level of functional reserve and cognitive capacity high enough to allow them to perform the programmed exercise intervention. A trained research assistant conducted a screening interview to determine whether potentially eligible patients met the following inclusion criteria: age ≥ 75 years, Barthel Index score ≥ 60 points, able to ambulate (with/without assistance), and to communicate and collaborate with the research team. Exclusion criteria included the expected length of stay < 6 days, very severe cognitive decline (ie, Global Deterioration Scale score = 7), terminal illness, uncontrolled arrhythmias, acute pulmonary embolism and myocardial infarction, or extremity bone fracture in the past 3 months. After the baseline assessment was performed, participants were randomly assigned following a 1:1 ratio, without restrictions, to an exercise intervention (n = 54) or usual-care group (n = 49). The randomization sequence was generated using www.randomizer.org. The assessment staff were blinded to the main study design and group allocation. Participants were explicitly informed and were reminded not to discuss their randomization assignment with the assessment staff. The study followed the tenets of the Declaration of Helsinki and was approved by the local ethics committee (Complejo Hospitalario de Navarra Research, approval #23/2014). All patients or their legal representatives provided written consent prior to the start of the study.

Intervention

The intervention was conducted on 5 to 7 days per week and consisted of 2 daily 20-minute training sessions (morning and evening). Morning sessions included individualized supervised progressive resistance, balance, and walking exercises. Participants performed 3 exercises involving mainly lower limb muscles (squats rising from a chair, leg press, and bilateral knee extension) and 1 involving the upper body musculature (seated bench press). They were instructed to perform the exercises at a high speed to optimize muscle power output. Balance and gait retraining exercises gradually progressed in difficulty and included the following: semitandem foot standing, line walking, stepping practice, walking with small obstacles, proprioceptive exercises on unstable surfaces (eg, foam pad sequence), altering the base of support, and weight transfer from one leg to the other. The evening session consisted of functional unsupervised exercises using light loads (eg, knee extension and flexion, hip abduction) and walking along the corridor of the ACE unit, with a duration based on the clinical physical exercise guide "Vivifrail" (www.vivifrail.com/resources) (14). It was not possible to blind the participants, and so they were informed and reminded not to discuss their randomization assignment with the assessment staff.

Endpoints

The primary endpoint was the change in functional status from admission to hospital discharge, as assessed with the Short Physical Performance Battery (SPPB) (15) and the Barthel Index of independence during activities of daily living (ADLs) (16).

Secondary endpoints were: handgrip strength (dominant hand) (17); cognitive function, as assessed with the Mini-Mental State Examination questionnaire (score ranging from 0 [worst] to 30 [best]) (18); mood status (15-item Yesavage Geriatric Depression Scale, with the score ranging from 0 [best] to 15 [worst]) (19); quality of life (QoL) visual analog scale of the EuroQol–5 Dimension questionnaire, with a 0 (worst health state imaginable) to 100 (best health state imaginable) scale (20); and incident delirium (Confusion Assessment Method) (21). We also assessed other clinical outcomes such as the length of hospital stay and the incidence of falls during hospitalization, as well as the incidence of transfer to nursing homes, hospital readmission, and mortality over a 3- month follow-up after discharge.

Statistical analysis

We used intention-to-treat and per-protocol approaches. Between-group comparisons of continuous variables were conducted using linear mixed models, with time as a categorical variable. The models included group, time, and group by time interaction as fixed effects and participants as random effect. For each group, data are expressed as change from baseline (admission) to discharge. Between-group comparisons were performed with the Mann-Whitney U test for non-normally distributed quantitative data, mid-*P*-value exact test for rates, and χ^2 or Fisher's exact tests for categorical data. All comparisons were 2-sided, with a significance level of 0.05, except for the analysis of the primary endpoint, where the Bonferroni-Holm multiple test adjustment was applied. All statistical analyses were made with SPSS (version 20; IBM Corp, Chicago, Illinois) or R (version 3.2.2, R Foundation software).

Results

The flow diagram of study participants is shown in Fig. 1. A total of 103 diabetic patients were included in the analyses. No significant between-group differences were found for baseline demographic and medical characteristics (Table 1). The median length of stay was 8 days (interquartile range, 4) for both groups. There were no intervention-related adverse events, and no patient had to interrupt the intervention or had their hospital stay modified because of the study protocol.

The intervention provided significant benefits over usual care on the change of the SPPB and Barthel Index from baseline to discharge (Fig. 2). It also induced improvements in some secondary endpoints such as cognitive status, depression, QoL, and handgrip strength (Table 2). By contrast, no intervention effect was noted for incident delirium (Table 2) or for those endpoints assessed during the 3-month follow-up (Table 3).

Discussion

The present study shows that a multicomponent individualized physical exercise intervention is safe and effective for the prevention of functional and cognitive decline in acutely hospitalized older diabetic patients. In turn, no effects were found for other major outcomes such as length of hospital stay or incidence of readmission, transfer, or mortality at follow-up.

Avoiding the deleterious consequences of hospitalization on older adults and, particularly, on those with DM is of major relevance. However, evidence on the best practices for the management of diabetic patients during hospitalization is scarce (22). The presence of DM can exacerbate the collateral consequences of hospitalization, as these patients are at a high risk of having sarcopenia and frailty (7, 23). For instance, Mackenzie et al (7) recently reported that hospitalized older adults with DM are ~2 times more likely to be frail than those without diabetes. Although the underlying mechanisms remain to be elucidated, some have been proposed. Diabetes mellitus is associated with increased muscle wasting due to an impaired anabolic status caused by a reduction in the anabolic milieu produced by insulin, and to increased protein breakdown caused by the

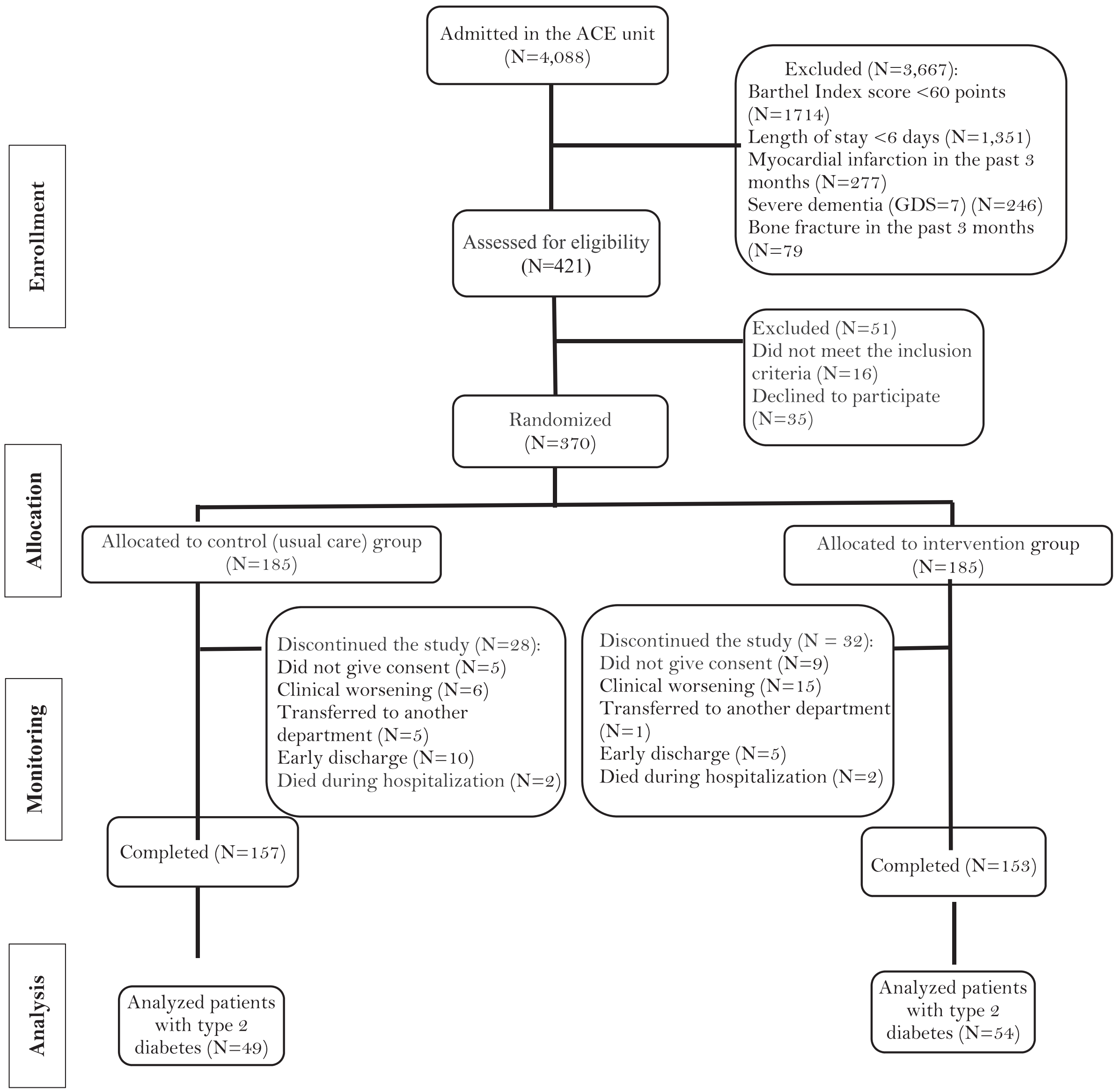

Figure 1. Study flow diagram.

proinflammatory status and the high levels of oxidative stress that are commonly observed in these patients (23–25). Moreover, patients with DM—particularly those who have undergone episodes of severe hypoglycemia—present with an increased risk of dementia (26), which has also been linked to the oxidative stress and proinflammatory status that are frequently found in these patients (27, 28). In this regard, some clinical trials have reported beneficial effects of exercise interventions on the functional and cognitive status of acutely hospitalized elderly adults (12, 13), but to the best of our knowledge, no previous study has specifically focused on diabetic patients. Therefore, the present study supports the potential role of in-hospital short-term exercise training as a cornerstone of the treatment of diabetic patients during acute hospitalization.

The benefits observed here for diabetic patients are in line with those previously reported for hospitalized adults with different comorbidities. For instance, in the main trial, in which the patients of the present study were also included, similar findings were reported for elderly adults with different conditions, including cardiovascular, neurodegenerative, and respiratory ones (12). Although this might be seen as a lack of novel results, these findings are of major clinical relevance, as they confirm that in-hospital interventions can be effective even in a population at particular risk of frailty and hospitalization-related negative outcomes such as elderly diabetic patients. Moreover, the positive effects of an individualized exercise intervention in acutely hospitalized older adults with DM to reverse the functional decline were higher than those observed in the main trial for elderly adults with different conditions

Table 1. Main demographic, clinical, functional, and endpoint data at baseline by group[c]

	Control (n = 49)	Intervention (n = 54)	*P*-value
Demographic data			
Women, N (%)	28 (57.1%)	25 (46.3%)	0.36[a]
Age, mean ± SD yrs	86 ± 5	87 ± 4	0.300[b]
Body mass index, mean ± SD kg/m^2	28.6 ± 5.2	27.7 ± 4.3	0.417[b]
Clinical data			
Concomitant diseases, N (%)[d]	10(4%)	11 (4%)	0.770[b]
CIRS score, median (IQR)[e]	14 (8)	15 (7)	0.788[3]
MNA score, median (IQR)[f]	25 (4)	25 (5)	0.291[3]
6-meter gait velocity test, mean ± SD	15.4 ± 6.8	14.2 ± 5.7	0.392[b]
1RM leg press, mean ± (SD) kg	63 ± (29	59 ± 23	0.419[b]
1RM chest press, mean ± (SD) kg	27 ± 13	25 ± 11	0.398[b]
HbA1c, mean ± SD	7.5 ± (1.3)	7.3 ± 1.4	0.610[b]
Primary endpoints			
SPPB scale, mean ± SD score[g]	4.8 ± 2.7	4 ± 2.3	0.141[b]
Barthel index, mean ± SD score[h]	79 ± 17	83 ± 17	0.385[b]
Secondary end point measures			
MMSE, mean ± (SD) score[i]	22 ± 5	22 ± 5	0.951[b]
GDS, mean ± (SD) score[j]	3.6 ± 3.0	3.6 ± 2.1	0.982[b]
QoL (EQ-VAS), mean ± (SD) score[k]	56 ± 22	56 21	0.933[b]
Delirium (CAM), N (%)[l]	8 (18.6%)	5 (12.2%)	0.610[b]
Handgrip, mean ± (SD) kg	16 ± 6	18 ± 6	0.346[b]
Admission reason, N (%)			
Pulmonary	19 (38.8%)	22 (40.8%)	0.995[a]
Cardiovascular	10 (20.4%)	16 (29.6%)	0.046[a]
Neurological	2 (4.1%)	2 (3.7%)	0.685[a]
Musculoskeletal	2 (4.1%)	2 (3.7%)	0.685[a]
Genitourinary	4 (8.2%)	2 (3.7%)	0.581[a]
Other	12 (24.5%)	10 (18.5%)	0.616[a]

Abbreviations: 1RM, one repetition maximum; CAM, Confusion Assessment Method; CIRS, Cumulative Illness Rating Scale; EQ-VAS, visual analogue scale of the EuroQol questionnaire (EQ-5D); GDS, Yesavage Geriatric Depression Scale; HbA1c, Glycated Hemoglobin; IQR, interquartile range; MNA, Mini-nutritional Assessment; MMSE, Mini Mental State Evaluation; QoL, quality of life; SD, Standard Deviation; SPPB, Short Physical Performance Battery.

[a] Chi-squared test.

[b] Unpaired Student's *t*-test.

[c]No statistically significant differences were found between groups (all $P > 0.10$).

[d]The most prevalent diseases were hypertension, heart failure, dyslipidemia, osteoarthritis, cardiac arrhythmias, chronic obstructive pulmonary disease, chronic gastritis/gastroesophageal reflux, chronic kidney disease, and urinary incontinence.

[e]The CIRS scale evaluates individual body systems, with a score ranging from 0 (best) to 56 (worst).

[f]The Mini-Nutritional Assessment score ranges from 24 to 30 (normal nutritional status), 17 to 23.5 (risk of malnutrition), or < 17 (malnourished).

[g]The SPPB scale ranges from a score of 0 (worst) to 12 (best).

[h]The Barthel Index score ranges from 0 (severe functional dependence) to 100 (functional independence).

[i]The Mini-Mental State Examination score ranges from 0 (worst) to 30 (best).

[j]The Yesavage Geriatric Depression Scale score ranges from 0 (best) to 15 (worst).

[k]Measured using the visual analog scale of the EuroQol Questionnaire–5 Dimensions, with a score ranging from 0 (worst health state imaginable) to 100 (best health state imaginable).

[l]Measured using the Confusion Assessment Method, with feature 1 indicating acute onset and fluctuating course; feature 2 = inattention; feature 3 = disorganized thinking; and feature 4 = altered level of consciousness; and with diagnosis of delirium requiring the presence of both features 1 and 2 and either 3 or 4.

(12). However, it must be noted that most in-hospital interventions to date have consisted of mobility exercises (eg, walking). In this regard, although mobility exercises alone might be beneficial for the improvement of functional status in hospitalized patients (29, 30), some authors have found no benefits with this type of intervention (31, 32). In turn, multicomponent interventions such as those applied here (including both mobility and strengthening exercises) might provide greater benefits on the functional status of hospitalized patients (33), which is supported by recent trials (29, 30). Indeed, this type of intervention has been proposed as the most effective option for the improvement of functional status and QoL in old and frail diabetic patients (3).

Also noteworthy is the lack of significant effects for major outcomes assessed during the follow-up, such as readmission and mortality rates, which is in line with previous research (29, 30). In turn, other authors have recently reported a lower incidence of negative events post-discharge, including a trend towards a lower mortality rate (5% vs 19% for the exercise and control group, respectively) (34) in older inpatients who had participated in an exercise intervention. Moreover, recent research has shown that those patients with a greater functional decline from admission to discharge were at a higher risk of presenting poorer outcomes during a 3-month follow-up, including a worse functional status and a greater incidence of falls (35, 36). Thus, further research is needed to confirm whether the exercise-induced benefits observed at discharge have any influence in the middle- or long-term.

Our study has some limitations, notably the relatively small sample size and the fact that it was conducted in only 1 hospital, which might limit the generalizability of our findings. On the other hand, some strengths should be acknowledged. To the best of our knowledge, this is the first study that has analyzed the effects of exercise on older patients with DM in the acute hospital setting (vs long-term care or rehabilitation settings). Moreover, older patients with multiple comorbidities are often excluded from exercise studies, whereas patients in the present study had a mean of 9 comorbidities (including dementia).

Conclusions

An individualized multicomponent short-term exercise training program was safe and effective for the prevention of the functional and cognitive decline commonly observed with acute hospitalization in elderly diabetic adults, although it exerted no influence on other endpoints assessed after discharge such as readmission and mortality rates. Although more research is needed, these

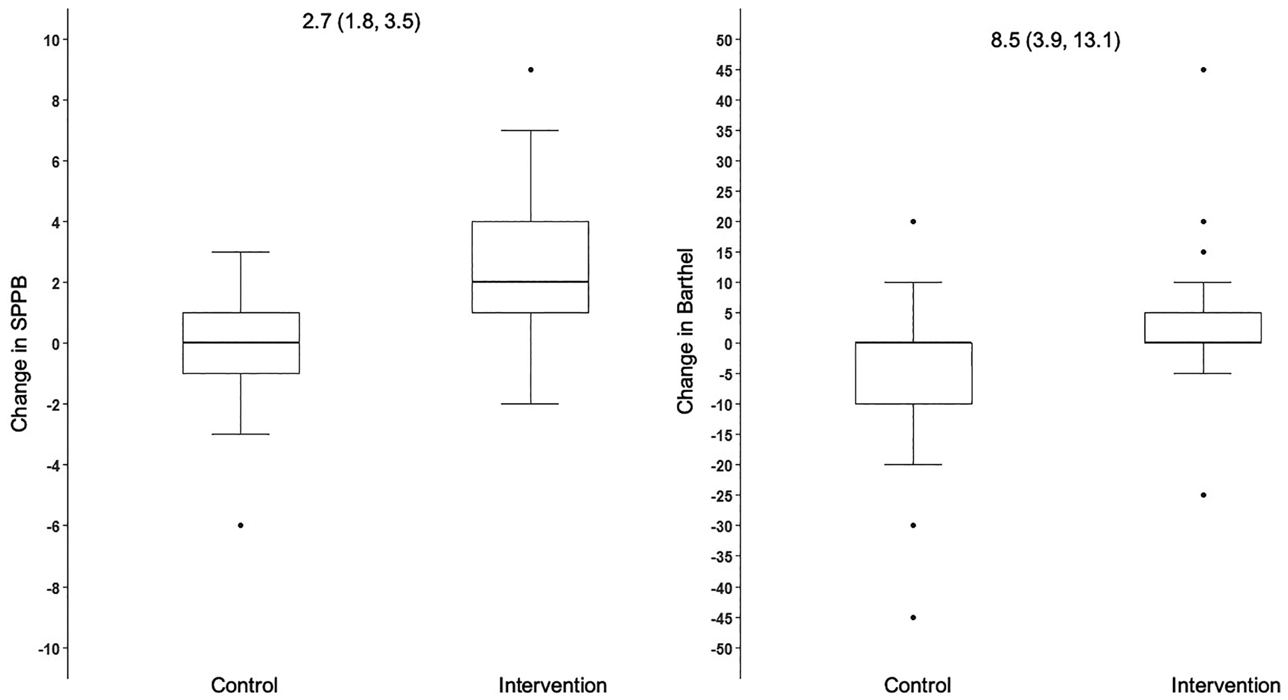

Figure 2. Change from baseline (admission) to discharge in the Short Physical Performance Battery (**A**) and in the Barthel index (**B**) by group. In the box plots, the box indicates Q1 to Q3; the horizontal line within the box indicates the median; the error bars indicate the 1.5 × interquartile range; and the solid circles beyond the error bars indicate the outliers. Differences between the treatment groups were tested using linear mixed models, with time as a categorical variable.

Table 2. Results of primary and secondary endpoints by group[a]

Variable[b]	Control	Intervention	Between-group Difference (95% CI)	*P*-value between Groups
Primary endpoints				
SPPB scale (balance, gait ability, leg strength)	-0.1 (-0.7, 0.5)	2.6 (2.0, 3.2)	2.7 (1.8, 3.5)	**<0.001**
Barthel index (ADLs)	-4.8 (-8.2, -1.5)	3.7 (0.5, 6.8)	8.5 (3.9, 13.1)	**<0.001**
Secondary endpoints				
MMSE	0.1 (-0.6, 0.7)	1.7 (1.0, 2.3)	1.6 (0.7, 2.6)	**0.001**
Depression (GDS)	0.7 (0.1, 1.2)	-1.5 (-2.1, -1.0)	-2.2 (-3.0, -1.4)	**<0.001**
QoL (EuroQol-5D)	4.6 (-2.0, 11.3)	14.7 (8.5, 21.0)	10.1 (1.0, 19.3)	**0.033**
Incident delirium (CAM)	14.0%	12.2%	OR 1.2 (0.3, 4.2)	0.811
Handgrip strength (kg)	-0.7 (-1.4, 0.1)	1.8 (1.0, 2.5)	2.5 (1.4, 3.5)	**<0.001**

Bold values denote statistical significance.
Abbreviations: ADLs, activities of daily living; CAM, Confusion Assessment Method; CI, confidence interval; EurolQol-5D, EuroQol Questionnaire–5 Dimensions; GDS, Yesavage Geriatric Depression Scale; MMSE, Mini-Mental State Examination; OR, odds ratio; QoL, quality of life; SPPB, Short Physical Performance Battery.
[a]All data, except for CAM, were derived from a linear mixed-effects model. For each group, data are expressed as a change from baseline (admission) to discharge, determined by the time coefficients (95% CI) of the model. For example, for the SPPB scale, -0.1 corresponds to the coefficient estimated from the model. The between-group difference was determined with time by group interaction coefficient. For CAM, data are the proportion of patients who developed delirium.
[b]Explanations of the scales used are given in the footnotes of Table 1.

findings—along with the widely proven benefits of exercise on cardiometabolic risk factors in individuals with DM—support the routine implementation of physical exercise for the management of hospitalized diabetic patients.

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Table 3. Results of secondary endpoints indicative of adverse events or hospitalization

Endpoint	Control (N = 49)	Intervention (N = 54)	*P*-value between Groups
Length of hospital stay, median (IQR) of days	10.1 (4.0)	9.4 (4.0)	0.442[a]
Falls during hospitalization, % (% per group experiencing ≥ 1 fall)	0%	0%	–
3-month hospital re-admission rate (10 people per 3-months), median (IQR)	2.4 (1.2, 4.4)	3.1 (1.7, 5.1)	0.565[c]
3-month mortality, %	8 (16.3%)	9 (16.7%)	0.963[b]
Transfer, %			
Home	44 (89.8%)	50 (92.6%)	–
Institutionalization	0	0	0.733[d]
Other	5 (10.2%)	4 (7.4%)	–

Abbreviations: ADL, activities of daily living; IQR, interquartile range.
[a]Mann-Whitney U test.
[b]Chi-squared test.
[c]Mid-p test.
[d]Fisher exact test.

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Additional Information

Correspondence and Reprint Requests: Mikel Izquierdo, PhD, Department of Health Sciences, Public University of Navarra, Av. De Barañain s/n 31008 Pamplona (Navarra), Spain. E-mail: mikel.izquierdo@gmail.com.

Disclosure Summary: The authors have nothing to disclose.

Data Availability: Some or all datasets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

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