JPFSM: Study Protocol

Tele-guidance for intensive physiotherapy in older patients with type 2 diabetes: a study protocol for randomized controlled trial

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Received: April 24, 2019 / Accepted: August 29, 2019

Abstract A recent trend in Japan is the increasing number of older patients with diabetes. Treatment for diabetes mellitus in older patients involves a wide variety of strategies, not only for better glycemic control, but also for the prevention and improvement of locomotive syndrome, sarcopenia, and frailty. Previous studies have shown that tele-guidance treatment interventions are effective for weight loss and increase in physical activity, but their effects on locomotive syndrome, sarcopenia, and glycemic control have not been examined. The objective of this study is to assess the efficacy of tele-guidance for intensive therapeutic interventions for diabetes mellitus in older patients, carried out by a qualified physical therapist with diabetes-specific qualifications and knowledge. This multi-center study, including 6 hospitals in Japan, is a prospective, parallel-group, single-blinded, randomized controlled trial. A total of 78 patients will be registered based on our preliminary studies. Patients aged 65–89 years with type 2 diabetes mellitus will be assigned randomly to intensive intervention and control groups. The effectiveness of 6 months of intervention will be verified by a physical therapist. The primary outcome measure will be the change in isometric knee extension force (KEF), whereas the secondary outcomes will be changes in skeletal muscle mass, motor function, glycemic control, and satisfaction with the treatment. When prescribing exercise therapy to older patients with diabetes mellitus, the various risks associated with exercise should be taken into consideration. Therefore, this study has been designed to establish the efficacy of intensive physiotherapy programs in older patients with diabetes mellitus. Provided that this study shows the effectiveness of tele-guidance in improving physical function and glycemic control, it can be a new intervention strategy for exercise therapy in older diabetes patients.

Keywords : randomized controlled trial (RCT), older patients with type 2 diabetes, intensive physiotherapy, tele-guidance, exercise therapy

Introduction

The prevalence of type 2 diabetes is increasing globally, and the International Diabetes Federation has predicted that the number of people with diabetes will increase

from 366 million to 552 million by 2030¹⁾. Importantly, the prevalence of diabetes in Asia is rapidly increasing, as 60% of the world's diabetic population is Asian²⁾. Japan has become the country with the fifth largest number of diabetic patients worldwide³⁾. The increasingly large population of older individuals is also becoming a serious problem in Japan. According to a report by the Ministry of Internal Affairs and Communications, by 2025, older individuals will make up approximately 30% of the overall Japanese population⁴⁾. Given this context, therapeutic interventions for older patients with diabetes mellitus will be important and are predicted to become more common in future clinical practice.

Older patients with diabetes mellitus are reported to

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experience impaired insulin action for various reasons, such as a decreased ability to secrete insulin, changes in body composition including increased visceral fat and decreased muscle mass, and reduced physical activity^{5,6)}. In these patients, the increased insulin resistance is associated with locomotive syndrome⁷⁾, sarcopenia⁸⁾ and frailty⁹⁾, all leading to muscle weakness¹⁰⁾. These conditions predispose a patient to become bedridden. Treatment for diabetes mellitus in older patients involves a wide variety of strategies, not only for better glycemic control, but also for the prevention and improvement of locomotive syndrome, sarcopenia, and frailty through proactive intervention by exercise therapy. While aerobic exercise is well known to improve glycemic control, insulin resistance and cardio-pulmonary function^{11,12)}, resistance exercise is known to increase muscle mass and muscle strength^{13,14)}. However, how these exercises should be performed by older individuals, considering the geriatric syndrome characteristics and the decline in a variety of physical functions, has not been well delineated. Therefore, individualized exercise intervention becomes important. However, it is extremely difficult for a physical therapist with sufficient experience and skills to directly and frequently intervene in a large number of older diabetes patients. We therefore examined the effect of exercise intervention by tele-guidance using telephone calls and e-mail.

Previous studies, in which regular assistance with treatment was provided to older patients through tele-guidance^{15,16)}, have demonstrated efficacy (reduced body

weight and increased physical activity) in subject groups of a wide range of ages. However, these studies did not investigate the effects of interventions on locomotive syndrome, sarcopenia, and glycemic control. The intervention method to be used in this study has several advantages. It is not time-consuming and can, therefore, be performed easily even during busy periods of work, making it adaptable for everyday medical practice. It also creates an environment in which patients undergoing treatment at home can receive specialist medical support at any time over the phone or via e-mail, without the need for a hospital visit. We believe that with this strategy, the patients will be willing to continue with their treatment, ultimately leading to improved patient satisfaction and higher rates of compliance with exercise therapy.

The objective of this study is to have a qualified physical therapist with diabetes-specific qualifications and knowledge assess the efficacy of intensive therapeutic interventions for diabetes mellitus in older patients. In this study, regular assistance with treatment will be provided to older patients through telephone calls and e-mail.

Materials and Methods

Study design

This will be a multicenter, prospective, parallel-group, single-blind, randomized controlled trial (RCT) that will include older Japanese patients with type 2 diabetes. The planned flow diagram for the study is presented in Fig. 1.

Fig. 1 Planned flow diagram

The patients will be randomly assigned to intervention and control groups, and the period of the study will be 6 months. Informed consent will be obtained from all participants before involvement in the study. Six hospitals (as of April 2019) that are actively engaged in medical treatment for diabetes will be involved in this study. In addition, there is also a possibility that additional facilities will be added during the research period. The study schedule is shown below: (1) hospital admission, (2) recruitment of study participants, (3) initial evaluation, (4) a common exercise program for both groups during hospitalization, (5) intensive intervention for one of the groups by tele-guidance after discharge, (6) interim appraisal, and (7) final assessment. The study protocol was approved by the KKR Takamatsu Hospital Ethics Committees (Approval number: E106). The original study protocol has been registered in the University Hospital Medical Information Network (UMIN000024416).

Study participants

Patients from 65 to 89 years old with type 2 diabetes will be recruited from 6 hospitals throughout Japan for this study. The inclusion criteria will be the ability to provide written informed consent to participate in this study. Patients with (1) bone and joint and/or cerebral vascular diseases, (2) highly restricted daily activities, (3) acute metabolic disorders, and (4) severe chronic complications of diabetes, will be excluded from the study. Additionally, patients who generally seem inappropriate for this study on the basis of investigation will also be excluded.

Calculation of sample size

The required sample size has been estimated on the basis of our preliminary studies. In this study, muscle training was conducted for 2 weeks in patients with type 2 diabetes to examine changes in muscle strength before and after. Sample size was calculated based on changes in KEF (Nm/kg). The difference to be detected is 9.9 (Nm/kg), with a standard deviation of 14.6. To detect an effect size of this magnitude, with 80% power, assuming a two-sided test at $\alpha = 0.05$, we have estimated that 71 participants will be required for this study. Taking into account dropouts (about 10%) we will be enrolling a total of 78 patients.

Randomization and blinding

The enrolled patients will be randomly assigned to intensive intervention and control groups in a 1:1 ratio by a computer. Randomization will be stratified on the basis of gender, age (65-74 or 75-89 years old)¹⁷⁾, and body weight¹⁸⁾ at baseline. Group affiliations for the study participants will be blinded, and randomization will be performed by Kansai University of Welfare Sciences.

Exercise program

Patients in the intensive intervention and control groups will be subjected to the same exercise therapy program.

Inpatients will be prescribed a moderate-intensity exercise program, using a bicycle ergometer for aerobic exercise and the Karvonen method for determining exercise load. The subjects will be required to perform aerobic exercises for 20 minutes, 5 days/week. They will also be required to perform resistance exercises using a rubber resistance band to train the main muscle groups of the upper and lower extremities (muscle groups of the shoulder, elbow, hip and knee joints) with an exercise load of 30%–50%, and one-repetition maximum. Resistance exercises will be performed 3 days/week, in 3 sets of 12 repetitions, and will be continued until the day of discharge. After being discharged, outpatients will be expected to continue the aerobic exercise program, wherein walking will replace the bicycle ergometer. They will also be given a free rubber resistance band and a pamphlet describing resistance exercises. The subjects will also be given a check sheet to record and monitor their progress with exercise therapy.

Physiotherapy tele-guide

Physical therapists participating in this study will have to meet the following requirements: (1) specialized in diabetes mellitus, with abundant experience in treatment of patients with diabetes, (2) qualified in all or any of the specialized areas of physical therapy, and (3) certified by both the Japanese Physical Therapy Association, and the Certification Board for Diabetes Educators in Japan.

1) Intensive intervention group

After receiving instructions for performing exercises, the intensive intervention group will be contacted by phone or e-mail once/week to (1) check on compliance with the prescribed exercise program, (2) answer questions about the exercise therapy and reconsider the program if required, (3) assess the subjects' responses and determine any behavioral changes using a transtheoretical model, (4) inquire about factors interfering with the continuation of exercise therapy (such as muscle or joint pain) and advise on countermeasures, and (5) provide suggestions for treatment methods other than exercise therapy (dietary and pharmacotherapies). Patients will be interviewed and evaluated at the hospital 3 months after discharge, to discuss issues that could not be addressed through phone or e-mail. Approximately 25 interventions will be scheduled for each patient by the end of the study.

2) Control group

The control group will not be given any instructions over the phone or by e-mail. The therapeutic intervention will be undertaken only at 3 months after discharge, whereupon the patients will be interviewed at the hospital to address the same five items described for the intervention group.

Clinical and laboratory measurements

We will collect data on gender, age, height, body

weight, body mass index (BMI), duration of type 2 diabetes, systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR), diet, medications, and laboratory test results. The levels of fasting plasma glucose (FPG), hemoglobin A1c (HbA1c), total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, serum insulin, serum creatinine, urinary albumin excretion, and estimated glomerular filtration rate (eGFR) will be measured using standard laboratory methods. A well-trained physical therapist will interview each patient to evaluate the level of physical activity, health-related quality of life, cognitive functions, satisfaction with diabetes treatment and exercise therapy, drinking, smoking, and other exercise habits. Diagnosis of type 2 diabetes mellitus will be based on the levels of FBG and HbA1c and will be performed according to the guidelines of the Japan Diabetes Society (JDS)¹⁹⁾. Diabetic retinopathy, nephropathy, and polyneuropathy will be diagnosed based on JDS guidelines. As described in our previous studies²⁰⁾, diabetic polyneuropathy is defined by the presence of at least two of the following symptoms: (1) dysesthesia, pain, and/or loss of sensation, (2) decreased or absence of Achilles tendon reflex, and (3) decreased vibratory sensation (≤ 10 sec).

Assessment of muscle strength, skeletal muscle mass, motor function, and satisfaction with treatment of diabetes

We will measure the handgrip strength and KEF. Handgrip strength will be measured using a handgrip dynamometer (T.K.K.5401, Takei Scientific Instruments Co., Ltd., Niigata, Japan), as described previously²⁰⁾. The subject will be in the standing position with the upper limb relaxed at the side, elbow fully extended, and palm inward. KEF will be performed using a hand-held dynamometer with belt stabilization (μ Tas F-1, Anima Inc., Tokyo, Japan), as described previously, and will be measured according to the method of our previous study²⁰⁾. All evaluations will be completed twice, and the best records from the left and right arms and legs will be averaged. Skeletal muscle mass will be measured using bioelectrical impedance analysis (DC-320, Tanita Co., Ltd., Tokyo, Japan). As parameters of motor function, we will perform the one-leg standing²¹⁾, functional reach²²⁾, 10m walking speed²³⁾, and the 25-question geriatric locomotive function scale (GFLS-25) tests²⁴⁾. Satisfaction with diabetes treatment will be investigated using the original questionnaire. The main survey items will include: (1) past experience receiving exercise instructions, (2) satisfaction with exercise instructions from a physical therapist, and (3) understanding the necessity of exercise therapy.

Outcome measures

The primary outcome of this study is to assess the KEF after 6 months of intensive intervention. Secondary outcomes will include changes in skeletal muscle mass, motor function, glycemic control, and satisfaction with the

treatment.

Statistical analysis

Descriptive analysis for the variables of interest will include means and standard deviation for continuous variables, and percentage for categorical variables. For comparison of parameters between the 2 groups, nonparametric or parametric tests based on the findings of the Shapiro Wilk test will be used for continuous variables, and the χ^2 test will be used for nominal variables. In addition, analysis of variance (ANOVA) will also be conducted. Subjects who satisfy the eligibility criteria of the study, will start the study treatment after randomization, and those for whom data are available will be included in the analysis. If the background between the two groups is biased, a general linear model based on the change in KEF in 6 months as a response variable and KEF at the baseline as the explanatory variable, will be used. All statistical analyses will be carried out using the IBM SPSS Statics 24 (Chicago, Illinois, USA) and JMP 12.2.0 software (SAS Institute, Cary, NC, USA).

Discussion

Aerobic and resistance exercises are well-known effective therapies for improving glycemic control in patients with diabetes mellitus. However, the recommended exercise therapy programs prescribe the uniform type, intensity, frequency and duration of exercise for all patients. Programs tailored specifically for individual patient needs are not well established. Recently, many studies have reported that patients with diabetes mellitus are at high risk of locomotion syndrome⁷⁾, sarcopenia⁸⁾ and frailty⁹⁾. Given the predicted rise in the incidence of diabetes mellitus among older patients, intervention by exercise therapy is anticipated to be used with increased regularity in the future. It is therefore vital that these programs be tailored specifically for older patients with diabetes mellitus.

Moreover, it is also important that the effectiveness of these programs be validated. This study aims to demonstrate the efficacy of a comprehensive exercise therapy intervention implemented and monitored by a physical therapist who specializes in exercise therapy for patients with diabetes mellitus. The intervention will be implemented by actively contacting the patients over the phone and via e-mail once a week not only to provide support with the exercise therapy, but also to offer advice on living conditions and issues related to the pathology and treatment of diabetes mellitus. The exercise guidance provided with clinical practice can monitor the implementation of the exercise therapy during hospitalization and can therefore immediately provide personalized instructions regarding changes in exercise programs. However, after being discharged from the hospital, it is much more difficult to monitor implementation of the exercise therapy, as well as provide support and follow-up. In fact, it is reported

Supplemental data 1. Tele-guidance for intensive physiotherapy in older patients with type 2 diabetes: a study protocol for randomized controlled trial

Japanese Clinical Sites and Physical Therapists

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Kimitsu Chuo Hospital, Kisarazu-city, Chiba: K. Kasahara.

Shuto General Hospital, Yanai-city, Yamaguchi: K. Mizoguchi.

Sanuki Municipal Hospital, Sanuki-city, Kagawa: Y. Murakawa, R. Hori.

Sakaide City Hospital, Sakaide-city, Kagawa: T. Okujyou, K. Miyamae, A. Tada.

that the continuation rate of exercise therapy is as low as 52.3%²⁵). Tele-guidance may therefore, be an effective intervention to improve the continuation rate of exercise therapy, as well as help with various age-related problems such as glycemic control and physical function. If we succeed in proving the effectiveness of tele-guidance, it may become one of the new exercise therapy strategies for older diabetic patients.

Acknowledgements

Six hospitals served as collaboration centers including KKR Takamatsu Hospital, Takamatsu City, Kagawa Prefecture; Chiba Central Medical Center, Chiba City, Chiba Prefecture; Kimitsu Chuo Hospital, Kisarazu City, Chiba Prefecture; Shuto General Hospital, Yanai City, Yamaguchi Prefecture; Sanuki Municipal Hospital, Sanuki City, Kagawa Prefecture; Sakaide City Hospital, Sakaide City, Kagawa Prefecture.

Funding

This work has been supported by the Japan Society for the Promotion of Science (JSPS) KAKENHI Grant Number JP15K01440. The JSPS had no role in the study design, data collection, analysis, decision to publish, or preparation of the manuscript. Publication of this paper received a research grant from Kansai University of Welfare Sciences and Hiroshima University Hospital.

Conflict of Interests

The authors declare that there are no sources of financial support or relationships that could pose a conflict of interest.

Author contributions

TN, HK and TK conceptualized the study design, protocol, and determined the study institutions. TN will collect and assemble the data. HO and YI will conduct the analysis and interpretation of data. HK wrote this study protocol manuscript. All authors have critically reviewed the report, commented on the drafts of the manuscript, and have approved the final report.

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