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Clinical impact of physical exercise on sleep disorder as assessed by actigram in patients with chronic pancreatitis: a study protocol for a randomised controlled trial

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ABSTRACT

Introduction In most chronic pancreatitis (CP) cases, malabsorption, pain, and weight loss are the leading clinical symptoms, which significantly worsen the quality of life (QOL) and decreased QOL in patients with CP can cause sleep disorder. There is a growing body of evidence that recognises the favourable effects of physical exercise (PE), however, there are limited data currently available concerning patients with CP undergoing PE. Actigram is a device for gathering objective sleep/awake data in the natural sleeping surroundings over an extended time period. In this study, we will aim to prospectively investigate the effect of PE on sleep disorder as assessed by actigram in patients with CP.

Methods and analysis This study is a non-double-blind randomised controlled trial. Study participants will be randomised into the PE group and the control group. When registering patients, precise assessment for nutritional status and daily physical activities will be undertaken in each study patient. In the PE group, physical activities equal to or higher than walking for 60 min/day should be strongly recommended. Sleep quality using actigram will be prospectively compared in the two groups. The primary endpoint is the activity index in actigram at 12 weeks.

Ethics and dissemination Ethical approval for the study was granted by the Institutional Review Board at Hyogo College of Medicine (approval number 2767). Results will be presented at relevant conferences and submitted to an appropriate journal following trial closure and analysis.

Trial registration number UMIN000029265 (https://upload.umin.ac.jp/); Pre-results.

INTRODUCTION

Chronic pancreatitis (CP) involves progressive inflammatory changes of the pancreas and it is a complex inflammatory disease condition characterised by irreversible injury to the pancreas.[1–5] In most CP cases, malabsorption, pain, and weight loss are the leading clinical symptoms, which significantly worsen the quality of life (QOL).[1–7] In particular, pain intensity and the frequency of pain attacks have been demonstrated to reduce QOL in patients with CP.[5] In Japan, CP is conventionally classified as the following three clinical phases depending on the clinical stage: compensated, transitional, and decompensated phases.[1] On the other hand, regular physical activity positively impacts the risk for disease onset and progression of several chronic diseases.[8–13] There is a growing body of evidence that recognises the favourable effects of physical exercise (PE) on mood states including stress, anxiety and depression, through physiological and biochemical mechanisms.[8–14] However, there are limited data currently available concerning patients with CP undergoing PE.

Decreased QOL in patients with CP can cause sleep disorder and poor sleep quality can further negatively impact QOL. The actigram is a medical device which reports body movement in daily life using an accelerometer.[15–17] Accelerometers are widely used to measure sleep-related behaviours, with the actigram being the most frequently used brand by researchers, and it is a non-invasive and cost-effective medical device used to assess the degree of sleep disorder compared with polysomnography as it is the size of a wristwatch and can be worn without hampering daily activities.[15–19]

As mentioned above, PE brings multiple health benefits to both healthy persons and

several patients with chronic diseases.[8–14 20 21] Despite these clinical benefits, few data are currently available for patients with CP undergoing PE on sleep disorder.[22] International consensus guidelines for patients with CP recognised a lack of specific and validated assessment tools of sleep quality.[1 5 23] Thus, there is urgent need for clarifying these problems. In this study, we will aim to prospectively investigate the effect of PE on sleep disorder as assessed by actigram in patients with CP.

PATIENT ELIGIBILITY CRITERIA

From the perspective of clinical practice, it should be emphasised that PE under poor nutritional status in patients with CP could be dangerous, given the fact that it could accelerate further protein catabolism and muscle mass decline.[1 23 24] When registering patients, precise assessment for nutritional status and daily physical activities will be thus undertaken in each study patient.

Inclusion criteria

1. Both sexes.
2. Patients with CP aged 20 years or more. Diagnosis for CP will be based on the current Japanese guidelines.[1]
3. Aetiologies and disease severity for CP are not limited.

Exclusion criteria

1. patients with severe depression or psychiatric disorder such as those with high scores in Patient Health Questionnaire-9 score (10 points or more)[25];
2. patients with acute pancreatitis or those with such severe CP that participation in this study is anticipated to be difficult;
3. patients with severe underlying diseases such as advanced malignancies (including pancreatic cancer), severe infectious diseases, severe chronic heart failure and respiratory disorders;
4. pregnant or lactating female subjects;
5. patients who may be at a risk of falls;
6. patients who were judged not to be suitable for the study subjects from the perspective of the ability to participate in PE (such as those with difficulty in walking or exercise);
7. patients with history of surgery or endoscopic therapy for pancreatic diseases;
8. patients with severe pancreatic ascites or pseudocyst;
9. patients who are considered to be unsuitable for study subjects for other reasons.

STUDY PROTOCOL

Study design: non-double-blind randomised controlled trial

Our study participants are patients with CP. All CP stages (compensated, transitional, and decompensated) will be included. Pharmacotherapy and diet therapy for CP will be allowed. Study participants will be randomised into two groups: (1) the PE group and (2) the control group (regular observation group) (figure 1).

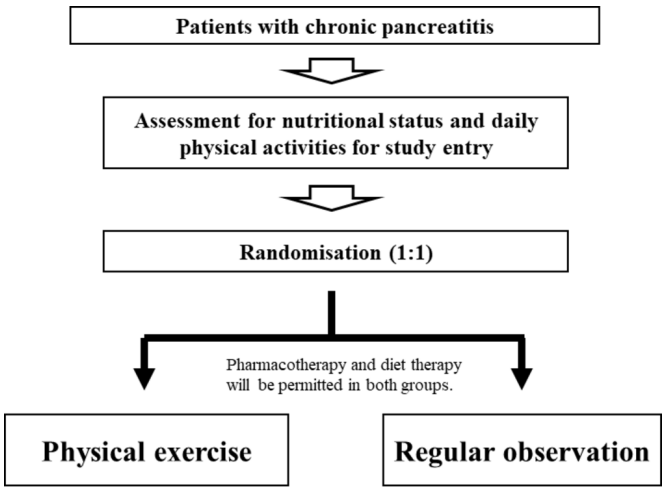

Figure 1 Study design.

Physical exercise

In the PE group, guidance for PE will be provided for each participant once a month at the outpatient guidance clinic. In the PE group, participants will also be instructed to perform exercises with ≥3 metabolic equivalents (mets; energy consumption in physical activities/resting metabolic rate) for 60 min/day and to perform exercises >23 mets per week.[8–13] In the PE group, physical activities equivalent to or higher than walking for 60 min/day should be strongly recommended. We will explain to the control group patients to do the same daily life as that before the trial participation. In both groups, pharmacotherapy such as protease inhibitors and pancreatic enzyme replacement therapy and diet therapy such as fat restriction diet in each underlying pancreatic disease will be allowed and we will ask all study participants for self-declare of daily amount of exercise.[1] Direct monitoring for exercise will not be undertaken.

Evaluation using actigram

Actigram is a medical device for gathering objective sleep/awake data in the natural sleeping surroundings over an extended time period.[15 16 26 27] The study subjects will be advised to wear a wrist actigram on their non-dominant wrist over a period of 3 days based on the manufacturer's information.[15 16 26 27] Evaluation by actigram will be carried out every 4 weeks. The follow-up period in each subject will be 12 months. At the same time points, data for laboratory testing, questionnaire, and clinical symptoms will be also gathered. Principally, study subjects will be advised to visit our hospital in an outpatient basis.

Data in the actigram will be downloaded into a dedicated computer program. The following five sleep-related factors will be used for assessment as mentioned elsewhere: (1) sleep onset latency; (2) wake after sleep onset (defined as the minutes awake during the sleep period after the beginning of sleep (the first two continuous

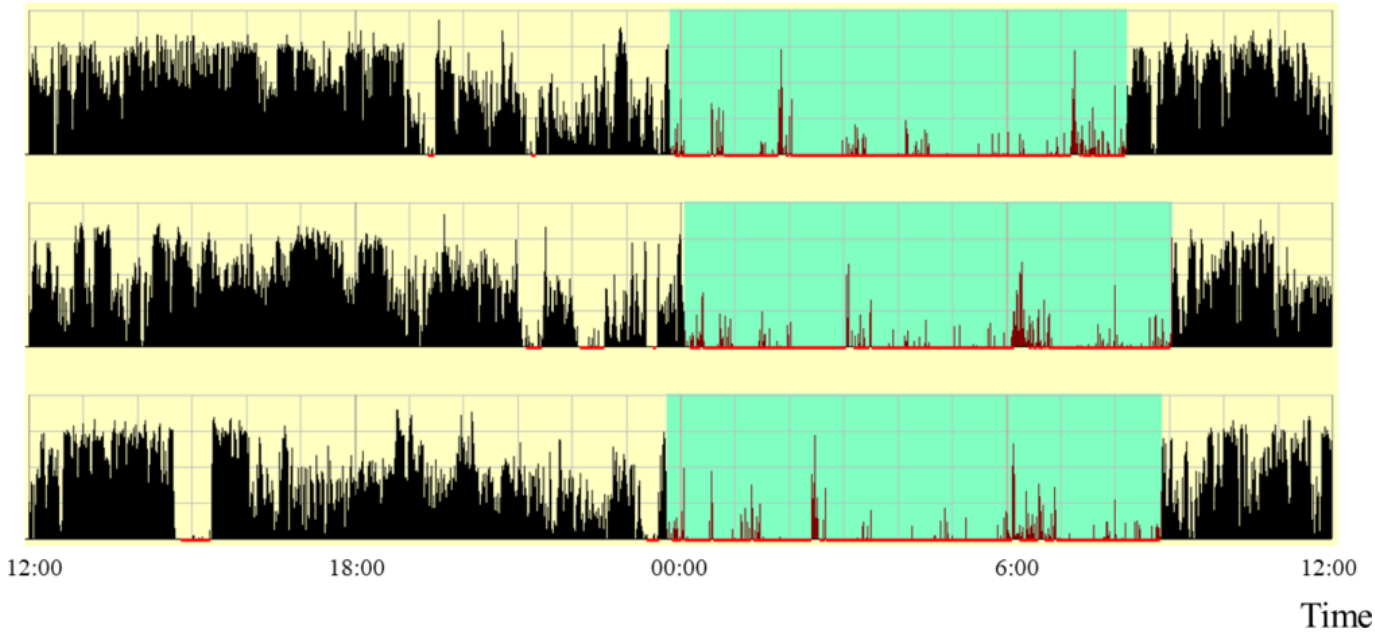

Figure 2 Representative case in actigram. Black thin line indicates activity level, red bold line indicates sleeping state and light blue rectangle indicates time in bed.

minutes scored as sleep)); (3) activity index (average amount of activity in sleep); (4) wake episodes (total number of wake counts between trying to start to sleep and wake-up times); and (5) sleep episodes in daytime (total number of sleep counts in daytime).[16] The increase in each score suggests the worse sleep quality. Activity index will be assessed as a primary outcome measure as it can well reflect sleep quality.[16] A representative case in actigram is presented in figure 2.

Study endpoints

Primary endpoints (confirmatory)

Activity index in actigram at 12 weeks. Activity index in actigram between baseline and at 12 weeks will be compared.

Secondary endpoints (exploratory)

Questionnaire survey

Sleep rhythm and depressed state in daily life will be assessed using questionnaire surveys (the Beck Depression Inventory, Second Edition,[28] and Pittsburgh Sleep Quality Index[29]).

Changes over time in baseline characteristics

Body weight, body mass index, white cell count, platelet count, serum albumin level, aspartate aminotransferase, alanine aminotransferase, total cholesterol, triglyceride, low-density lipoprotein, high-density lipoprotein, fasting blood glucose, HbA1c, homeostasis model assessment of insulin resistance, N-benzoyl-L-tyrosyl-p-aminobenzoic acid test, and so on.[1]

Follow-up and standard of care

During the observation period and after the end of this study, all patients will be seen in the clinic every 4 weeks to address complications of CP and other comorbidities. Compliance with pharmacotherapy will be particularly checked. Regular laboratory tests (haematology, biochemistry, and coagulation) will be needed at the study entry and at the end of study, and on an as-required basis.

Case registration period

From October 2017 to March 2021.

Data collection

A study assistant will gather data elements from patient medical records, including:

Baseline data:

a. sex and age
b. height and body weight
c. vital signs
d. drinking history and smoking history
e. cause for underlying pancreatic diseases
f. clinical stage of CP (compensated, transitional, or decompensated)
g. previous treatments and medicine
h. comorbid conditions
i. baseline laboratory data
j. presence or absence of ascites on radiologic findings.

Statistical methods

Descriptive statistics

Data will be subjected into JMP V.13 software (SAS Institute, Cary, NC) and all data will be checked to make certain their consistency. Data in each time point will be compared. Quantitative parameters will be compared by paired or unpaired t-test. Categorical parameters will be compared using Pearson χ^2 test or Fisher's exact test as applicable.

Sample size estimation

Based on our previous data of actigram, supposing that α error (type 1 error) is 0.05, detection power (β) is 0.8, difference in the two groups to be detected measured using actigram is 10, and SD of outcome is 10, the number of necessary cases in both groups will be 17 cases (total of 34 cases) in order to randomly allocate one to one.[16] Randomisation will be performed by our dedicated computer. We anticipate that a number of participants may drop out of the study; therefore, a total of 40 participants will be required to confirm our hypothesis.

DISCUSSION

The population of Japan has achieved the longest life expectancy in the world.[11 12] Japan is an ageing country and the clinical significance of PE has recently gaining much caution as PE brings numerous health benefits.[8–14]

Patients with CP have reduced life quality due to its related clinical symptoms.[6 7 24] Thus, it can be easily speculated that CP is closely associated with sleep disorder. However, there are limited data currently available concerning patients with CP undergoing PE on sleep disorder. Sleep disturbance in patients with CP may be a major concern. This study is the first prospective interventional study evaluating objectively the influence of PE on sleep disorder using actigram for patients with CP. From a clinical practice perspective, we highlight the potential safety risks of PE in undernourished patients with CP, as PE may risk promoting further protein catabolism and muscle mass loss. An adequate nutritional evaluation will be required prior to starting PE in our study cohort, and this study will be performed with full care.

One of the strong points of our study is that our study is planned as a randomised controlled trial (RCT). One study limitation is that this study will be based on a Japanese population, and additional examinations on different ethnic backgrounds are necessary to further verify the efficacy of PE on sleep disorder and extrapolate to other races. However, if the clinical efficacy of PE on sleep disorder for CP subjects is verified in this RCT, beneficial information will be provided for clinicians.

Ethics and dissemination

Research ethics approval

The study protocol, informed consent form and other submitted documents were reviewed and approved. Trial registration number is UMIN000029265 (https://upload.umin.ac.jp/); pre-results. No patient is registered at the submission of our manuscript.

Confidentiality

All data recorded on paper forms will be stored securely at the Department of Hepatobiliary and Pancreatic Disease, Department of Internal Medicine, Hyogo College of Medicine, Hyogo, Japan, in accordance with data protection procedures. Data collection forms identify participants only by their study ID. Participant consent forms, contact details and a single master copy linking participants' names and IDs will be held separately from other data. All data are held in locked filing cabinets in locked offices within our department, with limited access.

Dissemination policy

Final data will be publicly disseminated irrespective of the study results. Results will be presented at relevant conferences and submitted to an appropriate journal following trial closure and analysis.

Contributors KY designed the study and wrote the initial draft of the manuscript. HN and HE contributed to analysis and interpretation of data, and assisted in the preparation of the manuscript. YI, AI, YY, NI, YM, KH, CN, RT, TN, NA, YS, NI, TT, HI and SN contributed to data collection and interpretation and critically reviewed the manuscript.

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Competing interests None declared.

Patient consent Obtained.

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