


BMJ Open Study protocol to determine the effects of highly absorbable oral curcumin on the indicators of cognitive functioning: a double-blind randomised controlled trial

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ABSTRACT

Introduction Mild cognitive impairment (MCI) refers to a state in which cognitive functions, such as memory, have diminished but daily activities are largely unhampered. MCI is often overlooked but carries the risk of leading to development of dementia later. Curcumin is the main component of the natural herbal medicine turmeric.

Curcumin is widely used as a health food and is an antioxidant that has anti-inflammatory and anti-amyloid actions. The current trial was designed to determine the effects of curcumin on indicators of cognitive functioning.

Methods and analysis The current trial will be a single-centre randomised placebo-controlled double-blind parallel group trial. The participants will be 60 members of the general public with potential MCI, based on dementia screening using the Japanese version of the Mini Mental State Examination (MMSE-J). The investigational health food used in this trial will be a recently developed preparation for highly absorbable oral curcumin. This trial will determine the effects of the highly absorbable oral curcumin (brand name: curcuRouge) on the indicators of cognitive functioning, including the scores obtained with the MMSE-J, which is an interview-based measure of cognitive functioning, and the blood biomarkers that have been reported to be associated with dementia.

Ethics and dissemination Informed written consent will be obtained from all the participants. The Ethical Review Board of the National Hospital Organization Kyoto Medical Center approved the study protocol.

Trial registration number University Hospital Medical Information Network (UMIN000042471).

INTRODUCTION

Background of the condition of interest

Mild cognitive impairment (MCI) is a state in which individuals exhibit neither dementia nor normal cognitive functioning. Approximately 10% of individuals with MCI will eventually develop Alzheimer's disease or some other types of dementia. Studies conducted in

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ The current trial will be a single-centre randomised placebo-controlled double-blind parallel group trial.
- ⇒ This trial will investigate the effects of a newly developed preparation of a highly absorbable oral curcumin on indicators of cognitive functioning.
- ⇒ The aim of this trial will be to analyse the outcome of administering highly absorbable oral curcumin (brand name: curcuRouge) in members of the general public suspected of having mild cognitive impairment, in terms of its safety and its effects on the Japanese version of the Mini Mental State Examination scores and dementia-associated blood biomarkers.
- ⇒ The target sample size will be 60 participants (30 administered with placebo and 30 with the highly absorbable curcumin).

the USA, Italy, Germany, Canada and Finland reported that 11%–17% of the general population over the age of 60 years exhibits MCI.¹ In 2020, Japan's elderly population reached 28.7%, the highest in the world. Owing to the high proportion of Japan's ageing population, MCI is drawing attention as a major public health issue in Japan.²

Standard treatment

The pathogenesis of dementia is divided into three stages: preclinical Alzheimer's disease, MCI and dementia (Alzheimer's disease dementia). The focus of the management of dementia is to slow the progression of the disease. Management includes drug and non-drug therapy. Treatment drugs include cholinesterase inhibitors and antagonists for glutamate receptors of the N-methyl-D-aspartate type.

The period of MCI is considered to be a precursor to the onset of dementia, and a time when some cognitive functions, although not dementia, have declined and the risk of developing the disease has increased. It is important to take appropriate measures to reduce the risk of developing dementia during the MCI period.³

Cholinesterase inhibitors have been used to treat dementia. In 2005, one such cholinesterase inhibitor, donepezil hydrochloride, was reported to be effective in treating MCI. While donepezil hydrochloride prevented the onset of dementia in the first year, it did not inhibit the subsequent progression of MCI to dementia.⁴ So far, there is no scientific evidence indicating that donepezil hydrochloride inhibits the progression of MCI to dementia. Therefore, the active administration of cholinesterase inhibitors to treat MCI is not recommended. Lifestyle-related diseases such as hypertension, dyslipidaemia and diabetes are risk factors for MCI.³ A search for the last 5 years of systematic review, meta-analysis and randomised clinical research using 16 keywords such as “dementia”, “cognitive impairment”, “exercise” and “nutrition” suggested that exercise as well as dietary/nutritional interventions and multifaceted interventions for risk factors for angiopathy are effective.⁵

Curcumin: previous research

Curcumin is known to have physiological actions such as anti-tumour, anti-amyloid, anti-inflammatory and antioxidant activities.^{6,7} The authors demonstrated that the oral administration of curcumin inhibited the progression of heart failure in two rat models of chronic heart failure (hypertensive heart disease and myocardial infarction),⁸ and these results were reported by the media worldwide, including Columbia Broadcasting System (a major broadcaster in the USA). In a trial involving patients with hypertensive cardiac hypertrophy, the patients were administered a highly absorbable curcumin for 24 weeks, and echocardiography was used to evaluate the left ventricular function. The results indicated that the indicators of left ventricular diastolic function improved significantly. A patent application and another study indicated that a highly absorbable oral curcumin consumed by patients with mild chronic obstructive pulmonary diseases (COPDs) reduced the α 1-antitrypsin–low-density lipoprotein complex (AT-LDL) (an oxidised LDL) significantly compared with a placebo.^{9,10}

Curcumin inhibited amyloid deposition in animal experiments; therefore, it is expected to be effective in treating Alzheimer’s disease-type dementia. In addition, a systematic review that identified randomised placebo-controlled trials investigating the effects of curcumin supplementation on cognitive function in older people over the age of 50 years showed significant improvements in three out of five studies.¹¹ A placebo-controlled double-blind randomised controlled trial that was conducted recently in the USA indicated that the use of a highly absorbable oral curcumin (Theracurmin) prevented cognitive decline in people with MCI.¹² However, the

effects of curcumin have not yet been studied in Japanese population.

Curcumin is a principal component of natural turmeric. Curcumin is the main component of the natural herbal medicine turmeric. It is an antioxidant with anti-inflammatory and anti-amyloid effects.^{6,7} It is used as a health food in Japan, as a spice and colouring agent in food in India, as an herbal medicine in China and as a widely used safe colouring agent in the USA. If methods of using inexpensive, natural products to prevent cognitive decline are widely adopted in the future, it may help countries have a healthy, long-living population.

Benefit/risk assessment

MCI is an important risk factor for dementia. Dementia can develop despite the absence of obvious symptoms of cognitive decline. A systematic review suggests that curcumin provides a promising strategy for promoting cognitive function¹¹; however, effective methods of prevention are currently unknown, resulting in unmet needs. Clinical trials using highly absorbable curcumin have been conducted. The enrolment and the conduct of single-centre trials involving (1) mild COPD (UMIN000009139) and (2) impaired glucose tolerance (UMIN000007361) have been completed, and the findings from both trials have been published.^{10,13} The enrolment and the conduct of a joint clinical study on hypertensive cardiac hypertrophy (UMIN000014232) with the National Hospital Organization (NHO) network concluded at the end of March 2020. The safety profile of the trial preparation has been shown in these studies. The safety endpoint for the current trial will be determined based on the safety profile of the patients who undertook the trial preparation. Based on non-clinical and clinical data of the trial preparation, patients may benefit from the alleviation of MCI (a prodromal stage of dementia). In order to minimise anticipated adverse events, inclusion criteria, criteria for the modification of the treatment, criteria for discontinuing the trial preparation and a schedule for evaluating safety endpoints will be determined.

Objective of this trial

This trial will investigate a newly developed preparation of a highly absorbable oral curcumin. The aim of this trial will be to examine the effects of a highly absorbable oral curcumin (brand name: curcuRouge. curcuRouge is being sold commercially) in members of the general public suspected of having MCI, its effects on blood biomarkers and its safety.

METHODS AND ANALYSIS

Study protocol

An overview of the proposed study protocol is presented in [figure 1](#). The schedule of enrolment, interventions and assessments is illustrated in [table 1](#).

Design and sample size

The current trial will be a single-centre randomised placebo-controlled double-blind parallel group trial. A

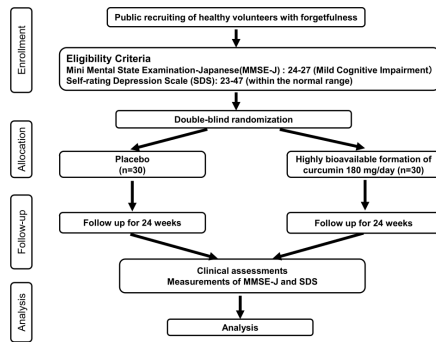


Figure 1 Overview of the study protocol.

placebo-controlled double-blind randomised controlled trial conducted in the USA indicated that highly absorbable oral curcumin (Theracurmin) prevented cognitive decline in people with MCI.¹² While the current trial design is based on that trial, it uses a different oral curcumin preparation (brand name: curcuRouge) that is absorbed more readily than Theracurmin. The current trial is being conducted to determine the effects of a highly absorbable oral curcumin (brand name: curcuRouge) on the indicators of cognitive functioning using the scores on the Japanese version of the Mini Mental State Examination (MMSE-J), which is an interview-based

measure of cognitive functioning, and blood biomarkers that have been reported to be associated with dementia.

The target sample size will be 60 participants (30 taking a placebo and 30 taking the highly absorbable curcumin).

Investigational health food (the trial preparation)

- ▶ The trial preparation: a highly absorbable curcumin capsule (curcuRouge) or a placebo capsule (both manufactured and supplied by Therabiopharma).
- ▶ The placebo preparation will contain cornstarch instead of curcumin.
- ▶ The trial preparation and placebo capsules will have the same external appearance, and their contents are not visible. The hue of the placebo will be adjusted to curcuRouge using food colouring.
- ▶ The dosage and method of administration: a 90 mg capsule of highly absorbable curcumin will be taken two times per day (morning and evening).
- ▶ The duration of administration: the trial preparation will be taken for 24 weeks.

Appropriateness of the dose

Highly absorbable curcumin (brand name: Theracurmin) is a health food that is sold. Previously, the Kyoto Medical Center conducted single-centre studies in which patients

Table 1 The schedule of enrolment, interventions and assessments

	Screening	Treatment		
	Day -56~-1	Day 1	Day 84±14	Day 168±14
Characteristics*	X			
Informed consent	X			
MMSE-J SDS	X		X	X
Confirmation of criteria	X			X
Registration	X			
Physical assessments BMI, blood pressure and pulse rate		X	X	X
Clinical assessments†		X	X	X
Serum biomarker‡		X	X	X
Treatment		<-----	-----	----->
Monitoring of adverse events		<-----	-----	----->
Monitoring of treatment compliance	X	<-----	-----	----->
Final assessment				X

*Characteristics: age, sex, educational background, lifestyle histories (alcohol, smoking), medical histories (eg, cardiovascular diseases, chronic obstructive pulmonary diseases, cancers, controlled hypertension, dyslipidaemia, diabetes, hyperuricaemia), histories of allergies.

†Clinical assessments: biochemical tests in blood and urine for monitoring of adverse events. Red cell counts; haemoglobin level; haematocrit; white cell counts, differential leucocyte counts; platelet counts; and levels of total protein, albumin, total bilirubin, alanine aminotransferase, aspartate aminotransferase, gamma glutamyl transferase, creatinine, urea, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein cholesterol, glucose, triglyceride, and C reactive protein. The biochemical data of the past 3 months are available.

‡Serum biomarkers: soluble lectin-like oxidised LDL receptor-1 (LOX-1), LOX-1 index (soluble LOX1×LOX-1 ligands containing apolipoprotein B), apolipoprotein A1, transthyretin, and C3 are measured by PreMedica, Japan. Serum amyloid A-LDL, α 1-antitrypsin-LDL and proinflammatory cytokines (IL-6, IL-1 β , IL-10, TNF- α , leptin, adiponectin) are measured by Health Science Research Institute West Japan, Co, Japan. The soluble fragment of triggering receptor expressed on myeloid cells 2 is measured in Kyoto Medical Center, Japan.

BMI, body mass index; IL, interleukin; MMSE-J, Japanese version of the Mini Mental State Examination; SDS, Self-rating Depression Scale; TNF- α , tumour necrosis factor α .

with mild COPD or impaired glucose tolerance were administered Theracurmin 180mg/day or a placebo for 24 weeks. In a mild COPD study, the patients' age was 70±6 years in the placebo group and 70±7 years in the Theracurmin group. In an impaired glucose tolerance study, the patients' age was 69±7 years in the placebo group and 70±6 years in the Theracurmin group. The results indicated the safety and efficacy of Theracurmin in patients with mild COPD or impaired glucose tolerance, as described in previous papers.^{10 13} A multicentre clinical study involving patients with hypertensive cardiac hypertrophies was conducted jointly with the NHO network. In that study, the participants were provided Theracurmin 180mg/day for 24 weeks or a placebo as a control. Based on the results of these studies, Theracurmin 180mg/day for 24 weeks is considered safe and efficacious. In addition, a study of excessive intake, in which Theracurmin 900mg/day was ingested for 4 weeks, showed that Theracurmin is clinically safe.¹⁴ curcuRouge is more readily absorbed than Theracurmin, with an area under the receiver operating characteristic curve of 3.4 times and a C_{max} 5.4 times that of Theracurmin.¹⁵ curcuRouge came to the market in September 2020. According to the Codex Alimentarius Commission, the acceptable daily intake of curcumin is 3mg/kg (180mg/day for an individual weighing 60kg). Based on the results of the previous studies on excessive intake of Theracurmin, taking curcuRouge at 180mg/day is considered to be safe.

Participants

The study's inclusion and exclusion criteria are listed in [box 1](#). The participants will meet all of the inclusion criteria. Individuals who meet any of the exclusion criteria will be excluded.

Concomitant therapy

This clinical trial will include members of the general public and not patients. However, an outpatient whose condition is stable can become a potential participant even if they are taking medications other than medication for dementia, which can be used concomitantly. However, the potential participant must have been using that medication for over 6 months prior to the date of consent, and there must have been no change in the regular medication or its dose for the 6 months prior to the date of consent. In principle, the basic treatment will not be modified or added for the duration of the trial. Nevertheless, participants who take oral steroids for a week or longer during the trial period will be excluded from this trial.

Prohibited concomitant medication/therapy

Concomitant medication will not be prohibited specifically except for antibiotics, oral steroids, multiple antiplatelet drugs or antithrombotic agents, as listed in the exclusion criteria. In principle, the dosing and dose of the concomitant medications will not be modified for the duration of the trial. If the dosage or dose of concomitant medication is modified due to a medical necessity

Box 1 Inclusion and exclusion criteria

Inclusion criteria

'People who are worried about forgetting things' will be recruited via posters or websites and interviewed using the Japanese version of the Mini Mental State Examination (MMSE-J) and a Self-rating Depression Scale (SDS). Members of the general public who meet all of the following criteria will serve as participants:

1. MMSE-J: scores between 24 and 27 points (mild cognitive impairment suspected).
2. SDS: scores between 23 and 47 points (normal range).
3. Individuals aged 50 years or over, regardless of sex.
4. Individuals from whom voluntary consent can be obtained in writing.

If an individual who is taking a medication for a condition other than dementia (such as a lifestyle-related disease) is recruited, he or she will be enrolled if he or she is active and his or her condition is stable.

Definition of active: ECOG (Eastern Cooperative Oncology Group) Performance Status: 0 or 1

Definition of stable condition:

1. No change in regular medication or its dose for 6 months prior to the date of consent.
2. No history of hospitalisation for 1 year prior to the date of consent.

Exclusion criteria

Individuals:

- ⇒ Who regularly consume health foods containing curcumin.
- ⇒ Who are allergic to curcumin.
- ⇒ Who are pregnant or breast feeding.
- ⇒ Taking medication for or receiving outpatient treatment for dementia.
- ⇒ Being treated for malignancy.
- ⇒ Taking an antibiotic or a steroid regularly.
- ⇒ Taking two or more antiplatelet drugs or an antiplatelet drug and another antithrombotic agent (anticoagulant, eicosapentaenoic acid or prostacyclin).
- ⇒ With histories of cerebral haemorrhages who are taking antiplatelet drugs.
- ⇒ Receiving oxygen therapy at home.
- ⇒ On dialysis for renal failure.
- ⇒ With severe liver dysfunction or cirrhosis.
- ⇒ With severe cardiac dysfunction.
- ⇒ Otherwise deemed ineligible for participation in this trial by a principal investigator or sub-investigator.

or if a new medication is required to be administered, the reason, name of the medication, dose and duration of administration will be listed in detail on the survey form (this provision does not apply in the event of a change in the warfarin dose or if an antibiotic or an analgesic is prescribed temporarily (for less than 2 weeks) to treat an acute case of a mild illness).

Discontinuation criteria

In the event of any of the occurrence of any of the following, the participants will cease taking the trial preparation:

- ▶ Adverse events.
- ▶ Discontinuation due to physician's decisions.
- ▶ Pregnancy.
- ▶ Protocol violations.
- ▶ Discontinuation by the participant.

Participants who discontinued only the trial treatment will continue to be followed up during the trial period (refer to the schedule for the type of data to be collected during the follow-up).

Discontinuation or conclusion of this trial

In the event of the occurrence of any of the following, the trial will be discontinued:

- ▶ Screening failures.
- ▶ Death.
- ▶ Loss to follow-up.
- ▶ Withdrawal due to physician decisions.
- ▶ Site terminated by the Institutional Review Board (IRB).
- ▶ Trial terminated by the IRB.
- ▶ Withdrawal by the participant.

If the trial is not discontinued and the last observation is completed, the trial will be then be considered to be concluded.

- ▶ Completed (epoch=follow-up).

Resumption of the trial treatment

If a participant's reason for discontinuing a trial preparation is addressed and a physician deems that the participant can resume taking the trial preparation, the participant will resume taking the trial preparation if no more than 4 weeks have passed since time of discontinuation.

Ethical approval

All the procedures performed will be in accordance with the ethical standards of the Institutional and National Research Committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This study was approved by the Kyoto Medical Center Ethics Committee (No 20-007).

Observation and testing schedule

Primary endpoint

The primary endpoint for this trial will be the scores obtained from the MMSE-J (an interview-based measure of cognitive functioning). The MMSE-J will be administered prior to the trial and 12 and 24 weeks after the start of the trial. This trial involved the preparation of a recently developed highly absorbable oral curcumin (brand name: curcuRouge). This trial will determine the effects of curcuRouge in members of the general public having MCI.

Secondary endpoints

The secondary endpoints for this trial will be the sTREM2, apolipoprotein A1, transthyretin and C3 levels and the presence of adverse events. This trial will use the aforementioned blood biomarkers that have been reported to be associated with dementia to determine the effects of curcuRouge on members of the general public suspected of having MCI. This trial will also examine the safety of curcuRouge in these people. Blood biomarkers will be measured in a blinded manner. The severity of adverse

events will be assessed using the Japanese version of the Common Terminology Criteria for Adverse Events V.4.0.

Exploratory endpoints

The exploratory endpoints for this trial will be the levels of the inflammatory and anti-inflammatory cytokines (C reactive protein, interleukin (IL-6), IL-1 β , IL-10, Monocyte chemoattractant protein-1, tumour necrosis factor α , leptin, adiponectin, etc), oxidised low-density lipoproteins (LDLs) (the LOX index, AT-LDL, serum amyloid A-LDL, etc), growth factors and their soluble receptors (vascular endothelial growth factor (VEGF), soluble VEGF receptors 2, etc), antibody markers (FLC (Serum Free Light Chain), nucleophosmin, etc), and results of immunity testing (the T cell count, the ratio of the CD4 T cell count to the CD8 T cell count, the naive T cell count, the ratio of the naive T cell count to the memory T cell count, the CD8+ CD28+ T cell count, B cell count, natural killer cell count and the coefficient of proliferation for T cells). These endpoints will be assessed to examine the effects of curcuRouge on other biomarkers in members of the general public suspected of having MCI.

This trial requires blood samples to measure the biomarkers. Blood will be collected from every participant prior to the trial and at 12 and 24 weeks after the start of the trial, and the serum will be preserved.

The samples remaining after the measurements will be retained by Kyoto Medical Center for 10 years after the completion of this trial. Upon completion of this trial, the names of the samples retained, the site where they are stored, the name of the sample control manager and the details of the consent obtained from participants will be reported to the head of the facility involved. Changes in this information will be reported in a similar manner. Once the period of retention is over, the samples will be discarded accordingly, while protecting personal information.

Statistical analysis

Sample size

A placebo-controlled double-blind randomised controlled trial that involved people with MCI who took highly absorbable oral curcumin (brand name; Theracurmin 180 mg/day) or a placebo for 18 months was recently conducted in the USA. This study allocated 21 patients in the Theracurmin group and 19 patients in the placebo group.¹² Theracurmin group showed significant improvement in cognitive outcome (Buschke CLTR (Constant Long Term Retrieval (CLTR)) from baseline by 20.3 (p=0.002). The difference of Buschke CLTR at 6 months from baseline was read 18 from the figure in the article and estimated 26 patients/group will need to show statistical significance ($\alpha=0.05$, power=0.8, two-sided test). The current trial will investigate curcuRouge, which is more readily absorbed than Theracurmin. And assuming that approximately 15% of the potential participants will drop out or be ineligible, 30 participants will

be needed in each group, thus necessitating a total of 60 patients.

Blind procedure

Before the start of the study, a statistician will assign numbers to the high-absorption curcumin and placebo using a random number table and send the allocation result to the allocation manager. The allocation manager or an assistant will label the boxes of the highly absorbent curcumin or placebo with the randomised number and send them to Kyoto Medical Center. The investigator will obtain written informed consent from the subjects and confirm that the subjects meet the entry criteria of the study and do not meet the exclusion criteria. The numbers allocated to high-absorption curcumin and placebo boxes will be unknown to the investigator. The investigator will administer the study food in the order of registration, starting with the smallest number.

Analysis sets

In all the evaluations of efficacy, the analysis will be based on the intention-to-treat principle. Regardless of the trial preparation intake, the analysis of the full analysis set (FAS) will be the main analysis and the per-protocol set (PPS) of the reference. Safety will be analysed using a safety analysis set (SAF). The sets will be defined as follows:

- ▶ FAS: the FAS will be the group of all the enrolled participants. If a serious violation of the trial protocol (failure to obtain consent or a major violation of trial procedures) occurs for a participant, that participant will be excluded.
- ▶ PPS: the PPS will be the group excluding participants from FAS who failed to meet the inclusion criteria or who meet the exclusion criteria, or who received a prohibited concomitant medication/therapy with respect to the provisions of the trial protocol (such as those regarding the trial treatment or concomitant therapy).
- ▶ SAF: the SAF will be the group of all enrolled participants, not including those who did not receive the trial treatment.

Methods of analysis

The details of the statistical analysis will be finalised before locking the database. A summary of the planned methods of statistical analysis that will be used to analyse the primary and secondary endpoints will be as follows:

The characteristics of the participants in both groups will be described using descriptive statistics, and then the distribution of MMSE-J scores (the primary endpoint) will be determined. In the primary analysis, the per cent of change in the MMSE-J score 24 weeks after the start of trial preparation with respect to the score prior to taking the trial preparation will be analysed, to compare the participants taking highly absorbable curcumin with those taking a placebo. In the secondary analyses, (1) the MMSE-J scores 24 weeks after the start of the trial will be

compared with the MMSE-J scores prior to the trial in each group (using a paired t-test), and (2) the MMSE-J scores of the participants taking a placebo and participants taking the highly absorbable curcumin will be analysed to examine the time-dependent changes in those scores prior to the trial and at 12 and 24 weeks after the start of the trial. A two-tailed α level of 5% and two-sided 95% CIs will be used.

In addition, the distribution of blood biomarkers (the secondary endpoints and exploratory endpoints) will be determined in a similar manner, and the primary and secondary analyses described earlier will be performed. All the safety analyses will be performed to ensure the safety of the population. The frequency of the adverse events will be compared in participants taking the placebo and those taking the highly absorbable curcumin, according to the type of adverse event. In addition, a stratified analysis using the participant's sex, age and MMSE-J score at screening will also be considered. When the number of cases reaches 20, an interim analysis will be performed to determine the validity of the sample size.

Early termination of this trial

This trial will be terminated early if any of the following situations occur:

- ▶ When it is determined that there are problems with the safety of the trial treatment or the placebo treatment based on serious adverse event reports of this trial or any safety information from sources other than from this trial.
- ▶ The completion of this trial will be deemed unlikely for reasons such as delays in participant enrolment or frequent deviations from the trial protocol.

Patient and public involvement

- ▶ Announce the research on posters or websites, and recruit research subjects.
- ▶ In this study, in order to protect the privacy of the subjects, the names, details of the current address, telephone numbers, email addresses, work information and school attendance information of the subjects will not be acquired as case data. Consideration should be given to protecting the privacy of research subjects even when the results of the research are published.
- ▶ Patients and the general public are not involved in the design of the study.
- ▶ The results of this research will be published at academic conferences or published within 2 years after the end of the research.

DISCUSSION

Dementia refers to a condition in which various causes, such as brain diseases or disorders, diminish cognitive functioning and hamper the activities of daily living. Dementia restricts the patient's autonomy in everyday life and his or her social life, and it can lead to a mentally unstable state, which can greatly affect family members (eg, the burden of caregiving and mental

strain). Alzheimer's disease-type dementia is the most common type of dementia, accounting for 60%–70% of all cases.¹⁶ As the cranial nerves degenerate and parts of the brain become atrophic, the Alzheimer's disease-type dementia progresses gradually. The Alzheimer's disease-type dementia is caused by the accumulation of amyloid β protein in the brain, the concentration of which increases with age. The amyloid hypothesis, which involves neuronal degeneration, is persuasive, but is yet to be completely elucidated. The worldwide population of patients with dementia is estimated to reach 76 million by 2030 and 135 million by 2050. According to the Hisayama study, there are an estimated 6 million people aged 65 years or older with dementia in Japan (as of 2020), and about 7 million people (approximately one in five elderly) are predicted to have dementia by 2025.¹⁷ The social costs of dementia are also increasing, reaching 3.9 trillion yen in the UK and 17.5–24 trillion yen in the USA. Those costs are estimated to reach about 14.5 trillion yen annually (medical costs: 1.9 trillion yen, long-term care costs: 6.4 trillion yen and informal care costs: 6.2 trillion yen) in Japan.¹⁸ Therefore, efforts to deal with dementia will be increasingly important, given the ageing population.

MCI is a state in which the memory diminishes, but not to the extent that it impacts everyday life, as in dementia. Individuals with MCI do not exhibit dementia or normal cognitive functioning. A study¹⁹ has reported that between 10% and 15% of individuals with MCI will develop Alzheimer's disease-type dementia within a year, and about half will develop it within 5 years.^{20 21} Thus, preventive intervention in the earlier stages of MCI is important to delay its progression to dementia. Nevertheless, a treatment that is effective for inhibiting the progression of MCI to dementia has not yet been established. Lifestyle-related diseases (hypertension, dyslipidaemia, diabetes, etc) are risk factors for MCI; however, at this current point in time, the only recommended treatment is a healthy lifestyle, for example, the management of lifestyle-related diseases and aerobic exercise.

Curcumin inhibited amyloid deposition in animal experiments; therefore, it is expected to be effective in treating Alzheimer's disease-type dementia. While a placebo-controlled double-blind randomised controlled trial that was recently conducted in the USA indicated that the highly absorbable oral curcumin (Theracurmin) prevented cognitive decline in people with MCI,¹² the effects of curcumin have not been studied in Japan; therefore, this current trial will determine these effects.

This trial will be a prospective randomised placebo-controlled double-blind parallel group trial to determine the effects of highly absorbable oral curcumin (brand name: curcuRouge) on the cognitive functioning of members of the general public suspected of having MCI. The MMSE is the most frequently used test to assess overall cognitive functioning worldwide.²² The score on the MMSE-J, which is the Japanese version of the MMSE (the contents are the same), will be the primary endpoint of this trial. A study has indicated that the MMSE-J can,

like the MMSE, serve as a valid and reliable test with which to screen for dementia.²³ In addition, the current trial will provide a preliminary evaluation of the blood biomarkers that have been reported to be associated with dementia as well as the inflammatory and anti-inflammatory cytokines. Curcumin has various physiological actions, such as anti-tumour, anti-amyloid, anti-inflammatory and antioxidant activities. This suggests that curcumin is effective in preventing different problems, including cognitive decline. Curcumin may, thus, contribute to a healthy, long-living population. However, curcumin is difficult to dissolve in water and has low bioabsorbability. Therefore, to enhance the physiological activity of curcumin, it is necessary to increase its absorption rate.¹⁶ Therefore, in this study, a highly absorbable curcumin preparation, whose safety has been confirmed, will be used. If an inexpensive, natural substance such as curcumin can prevent the progression of MCI to dementia, it may maintain the quality of life of patients, reduce the burden on their families, and reduce social burdens such as medical and long-term care costs, substantially.

In this research, 'people who are worried about forgetfulness' are widely recruited on posters or websites, but on top of that, those who are suspected of having MCI in the MMSE-J test, have a normal range in the Self-rating Depression Scale test and are over 50 years old are the research subjects. There is a possibility that the number of research subjects will be small.

ETHICS AND DISSEMINATION

Ethics approval and consent to participate

Informed written consent was obtained from all the participants. The Ethical Review Board of the NHO Kyoto Medical Center approved the study protocol. The approval number is 20-007 (16 November 2020).

Ethical and safety considerations and any dissemination plan

The data collected during this study belong to the NHO, and any publication or abstract of the study results requires the prior consent of the principal investigator's institution. The results of this study will be published in a conference presentation or article within 2 years of completion of the study. The collected data will be stored at the principal investigator's facility for at least 5 years after the completion of the study. Consideration will be given to protecting the privacy of the research subjects when destroying the records.

Trial status

At the time of the submission of this manuscript, the recruitment for this study is ongoing.

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