Trials

STUDY PROTOCOL

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The effects of diacylglycerol edible oil intervention in patients with chronic metabolic syndrome combined with asymptomatic hyperuricemia: study protocol for a multicenter, prospective, double-blind, randomized controlled trial

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Abstract

Background The aim of this study is to evaluate the efficacy and safety of diacylglycerol (DAG) edible oil intervention in patients with chronic metabolic syndrome complicated by asymptomatic hyperuricemia through a multicenter, prospective, double-blind, randomized controlled clinical trial.

Methods A multicenter, double-blind, and randomized controlled trial involving 176 patients was designed. All patients with chronic metabolic syndrome complicated by asymptomatic hyperuricemia who meet inclusion and exclusion criteria will be included in the study and will be randomized to either group A or group B. Group A will receive DAG-rich oil (≥ 80%) and group B will receive conventional cooking oil (triacylglycerol (TAG)-rich oil) for 12 weeks. Serum uric acid level is the primary outcome. Fasting blood glucose, 2 h postprandial blood glucose, fasting insulin, glycated hemoglobin, lipid profile, and average carotid intima-media thickness will be evaluated as the secondary outcomes. Blood routine, urine routine, liver enzymes, and electrocardiogram will be tested to assess the safety. The sample size for each group was calculated to be 88 cases.

Discussion We will evaluate the efficacy and safety of DAG oil compared with conventional TAG oil in patients with chronic metabolic syndrome with asymptomatic hyperuricemia. The dietary oil with superior efficacy and better safety will be recommended for reference use.

Trial registration Chinese Clinical Trial Registry ChiCTR2400085336. Registered on June 5, 2024.

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Keywords Diacylglycerol oil, Chronic metabolic syndrome, Asymptomatic hyperuricemia, Randomized controlled trial

Administrative information

Note: the numbers in curly brackets in this protocol refer to SPIRIT checklist item numbers. The order of the items has been modified to group similar items (see http://www.equator-network.org/reporting-guidelines/spirit-2013-statement-defining-standard-protocol-items-for-clinical-trials/).

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Name and contact information for the trial sponsor {5b}	Yong-hua Wang, email: yonghw@scut.edu.cn, Dan-ping Xu, email: xudanping@hotmail.com
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Introduction

Background and rationale {6a}

Chronic metabolic syndrome is a group of clinical syndromes with abdominal obesity, hyperglycemia/insulin resistance, dyslipidemia, and hypertension, which have a serious impact on body health. It is a combination of metabolic interrelated risk factors. These factors directly promote the occurrence of diseases such as atherosclerotic cardiovascular disease (ASCVD) and type 2 diabetes [1, 2]. Chronic metabolic syndrome is often associated with accelerated onset and progression of ASCVD, type 2 diabetes, stroke, hyperuricemia/gout, and chronic kidney disease [3].

Hyperuricemia is a metabolic syndrome caused by purine metabolism disorder. Serum uric acid exceeding its saturation in blood or interstitial fluid can form and deposit sodium urate crystals locally in joints, inducing local inflammatory response and tissue destruction, namely gout [4]. In recent years, the incidence of hyperuricemia in China has surged significantly, with the current prevalence rate climbing to 13% [5]. This condition is exhibiting a clear upward trajectory and is notably affecting a younger demographic [6]. Hyperuricemia has emerged as a prevalent metabolic disorder, following in the footsteps of diabetes [7].

Elevated serum uric acid (SUA) levels may be associated with cardiometabolic abnormalities, including hypertension and insulin resistance, which may lead to atherosclerosis and cardiovascular disease [5, 8]. Many evidences show that hyperuricemia and gout are independent risk factors for diseases such as chronic kidney disease [9], hypertension [10], cardiovascular and cerebrovascular diseases [11], and diabetes [12] and independent predictors of premature death [13]. Studies have found that serum uric acid level is a strong and independent predictor of metabolic syndrome, and hyperuricemia is more difficult to treat when associated with metabolic syndrome [14]. The incidence of hyperuricemia is partly associated with unbalanced diet [15].

In daily life, the main component of edible oil is TAG, which is formed by esterification of glycerol and three fatty acids. Compared with TAG, DAG is a product obtained by esterification of glycerol with two fatty acids [16] and is divided into 1,3-DAG and 1,2-DAG. DAG is widely found in natural animal and vegetable oils and is recognized as a safe food component, yet the content in natural edible oils does not exceed 10% [17], such as about 5.5% in olive oil, about 1% in soybean oil, and about 0.8% in rapeseed oil [16]. When the content of DAG esters in edible oil reaches a certain level (> 80%), its taste, appearance, and cooking performance are similar to that of traditional edible oil [18]. A number of studies have shown that oil rich in DAG reduce blood lipid levels and the accumulation of fat in the body [19–21].

However, to the best of our knowledge, the current clinical studies on DAG edible oil mostly focus on the impact on metabolic syndrome (mainly lipid metabolism abnormalities), and few clinical studies on the efficacy and safety of DAG edible oil in patients with chronic metabolic syndrome complicated with hyperuricemia. In this study, we hypothesized that DAG oil has an ameliorative effect on patients with chronic metabolic syndrome complicated with hyperuricemia, and the efficacy and safety will be observed through a multicenter, randomized, double-blind clinical study.

Objectives {7}

In this study, we will conduct a multicenter, prospective, double-blind, randomized controlled clinical trial to clarify the effects of DAG oil on patients with chronic metabolic syndrome combined with asymptomatic hyperuricemia, compared with traditional TAG oil. Its safety will also be evaluated. This study will provide reference for the application of DAG oil.

Trial design {8}

This study is designed as a multicenter, prospective, superiority, double-blind, randomized controlled clinical trial. A total of 176 cases were randomly divided into 2 groups according to 1:1 ratio, namely study group and control group. The trial includes a screening period ranging from days − 7 to 0, followed by a treatment duration of 12 weeks. The study design is shown in a flow diagram (Fig. 1).

Test oil

The DAG oil in this study was prepared from camellia oil using a whole-enzymatic method [22]. The DAG content in the prepared DAG oil was > 80%. TAG oil consists of camellia oil. The oil will be used in daily food cooking. When the content of DAG in edible oil reaches a certain level (> 80%), its taste, appearance, and cooking performance are similar to that of traditional edible oil [18]. Therefore, in the case of the same outer packaging, participants and researchers will not distinguish between them.

Methods: participants, interventions, and outcomes

Study setting {9}

This study will be conducted in China, focusing on the recruitment of participants from the four following distinguished hospitals: The Eighth Affiliated Hospital of Sun Yat-sen University, Shenzhen Hospital of Southern Medical University, The Third Affiliated Hospital of Guangzhou Medical University, and Shenzhen Hospital of Guangzhou University of Chinese Medicine (Futian). Our recruitment process will target patients who are seeking diagnosis and treatment at these institutions. To raise awareness and attract interested individuals, we will utilize a combination of promotional posters and leaflets. Prospective candidates who express interest in our study will be cordially invited to participate in a screening process. This will be a pivotal step in identifying individuals who meet our specific inclusion and exclusion criteria. Participants will be selected based on a set of criteria that have been meticulously designed to ensure the study's scientific rigor and relevance. These criteria will be applied consistently throughout the screening process.

Eligibility criteria {10}

Inclusion criteria

(1) Males and females aged 25–60 years.
(2) Abdominal obesity (that is, central obesity): waist circumference male ≥ 90 cm, female ≥ 85 cm.
(3) Fasting blood sugar ≥ 6.1 mmol/L or 2 h after glucose load blood sugar ≥ 7.8 mmol/L and/or diagnosed diabetes mellitus and treatment.
(4) Blood pressure ≥ 130/85 mmHg and/or recognized as hypertension and treated.
(5) Fasting TG ≥ 1.70 mmol/L.
(6) Fasting HDL-C < 1.04 mmol/L.

The above inclusion criteria must meet the three inclusion criteria (2, 3, and 5) or more. Meanwhile, the following conditions should be met: BMI < 32 kg/m^2, fasting blood glucose < 12 mmol/L, 2 h postmeal blood glucose < 16.7 mmol/L, HbA1c < 9.5%, blood pressure < 160/100 mmHg, fasting TG < 5.65 mmol/L, and fasting LDL-C < 4.9 mmol/L.

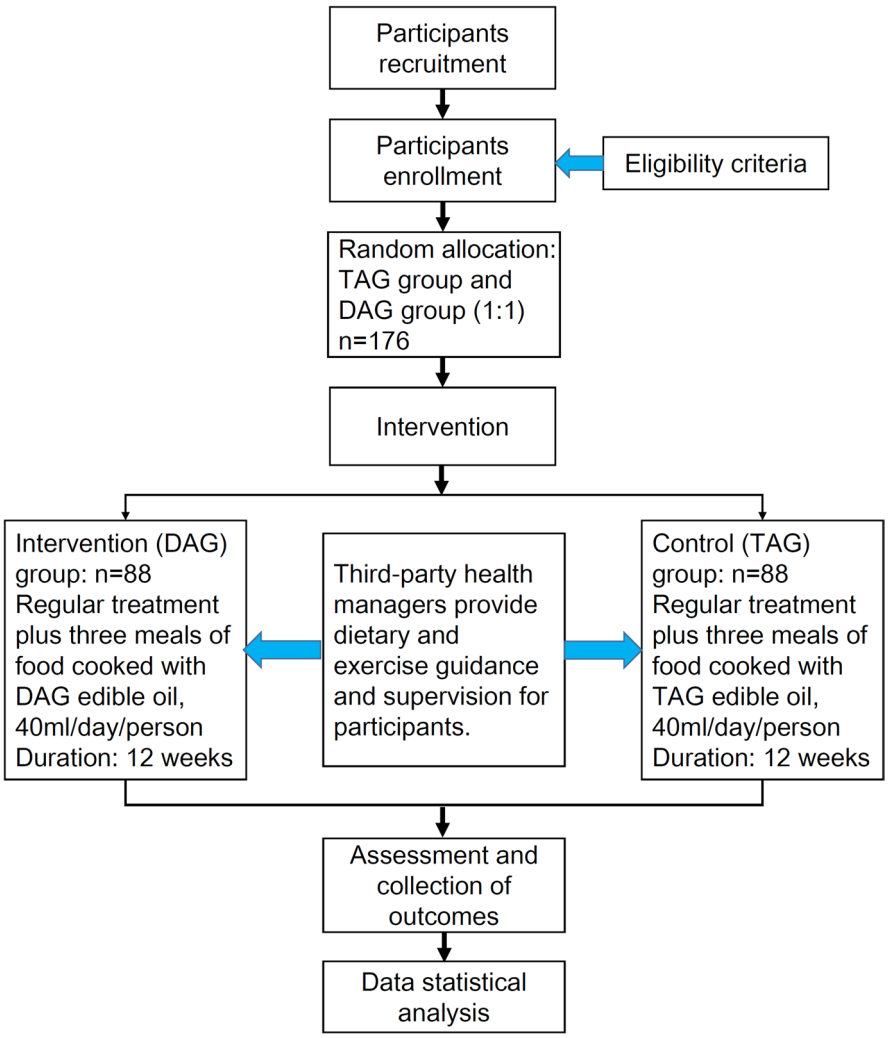

Fig. 1 Flow chart of this study

(3) No gout attack occurred when the serum uric acid level exceeded 420 μmol/L (7.0 mg/dL) for two times on different days.
(4) Willing to obey the doctor's intervention plan and cooperate with follow-up, informed consent and sign informed consent.

Exclusion criteria

(1) BMI ≥ 32 kg/m^2, fasting blood glucose ≥ 12 mmol/L, 2 h post-meal blood glucose ≥ 16.7 mmol/L, HbA1c ≥ 9.5%, blood pressure ≥ 160/100 mmHg, fasting TG ≥ 5.65 mmol/L, fasting LDL-C ≥ 4.9 mmol/L, meet one or more of the above.
(2) Patients diagnosed with type 1 diabetes mellitus or gestational diabetes mellitus or other types of diabetes mellitus, secondary hypertension, secondary hyperlipidemia or secondary hyperuricemia.
(3) The use of diuretics in drug combination.
(4) Advanced gouty arthritis, severe renal calculus, joint deformation.
(5) Those who have used hormone drugs in the last 6 months.
(6) Patients with previous history of pancreatitis, severe bone destruction, and severe limb dysfunction.
(7) Patients with cardiovascular and cerebrovascular, liver, kidney, hematopoietic, rheumatic immune system, retinopathy and other serious primary diseases, or known serious diseases affecting their survival (such as tumor or AIDS), or mental or legal disabilities (such as aspartate aminotransferase (AST), alanine aminotransferase

(ALT) > 1.5 times the upper limit of normal value, serum creatinine (Cr) > the upper limit of normal, serum creatinine clearance < 30 ml/min, and cardiac function above grade 3).

(8) Allergic to the ingredients of the test products.
(9) Women who are pregnant, planning to become pregnant, or breastfeeding.
(10) Have participated in or are participating in other clinical researchers within 1 month.
(11) The researchers judged that the participants should not participate in the experiment or were easy to lose.

Who will take informed consent? {26a}

Informed consent will be performed before participants undergo screening tests. The investigators will perform patient recruitment and informed consent. They will fully explain what is involved in the test, both orally and in writing. Participants will have ample time to consider whether to participate in the trial and to raise any concerns they have, and will be asked if they consent to the use of their data. Individuals who demonstrate a desire to participate in the trial will be cordially invited to a scheduled screening visit and they will be asked to sign and date consent prior to the study process. The investigator will receive a signed informed consent form from participants.

Additional consent provisions for collection and use of participant data and biological specimens {26b}

Blood (3 ml) and urine (3 ml) samples will be collected at weeks 1, 4, 8, and 12 for analysis to observe the effects of the test oil. These blood samples will not be analyzed until all participants have completed the trial intervention to eliminate the risk of blindness. If participants consent, additional study blood samples (3 ml), urine (3 ml), and stool from weeks 1, 4, 8, and 12 will be collected and stored at the same time for further genomic and biomarker studies.

Interventions

Explanation for the choice of comparators {6b}

TAG is the main component of edible oil in daily life, including soybean oil, peanut oil, olive oil, rapeseed, and camellia oil, and is often used in comparative studies with DAG oil [23].

Intervention description {11a}

Intervention group: regular treatment plus three meals of food cooked with DAG edible oil, 40 ml/day/person. Control group: regular treatment plus three meals of food cooked with TAG edible oil, 40 ml/day/person. Regular treatment includes pharmacotherapy for hypertension. Therapy duration: continuous use for 12 weeks. During the trial, the test cooking oils are provided free of charge by the project team. Concurrent use of medications outside the scope of this trial for treating the condition is prohibited. All participants maintain a healthy lifestyle, including weight control, regular exercise, dietary adjustments to reduce caloric intake, smoking cessation, and limiting alcohol, high-purine, and high-fructose diets. Each participant will be provided with a measuring cup to ensure a daily oil intake of 40 ml DAG or TAG oil. Dietary guidelines will be offered to each participant to ensure balanced intake of energy and fats.

Dietary guidelines: refer to "Chinese Dietary Guidelines (2016)" [24]:

- Diversify food intake with a focus on grains.
- Balance diet and physical activity to maintain a healthy weight.
- Increase consumption of vegetables, fruits, and dairy.
- Consume fish, poultry, eggs, and lean meats in moderation.
- Reduce salt, oil, sugar intake, and limit alcohol.

Criteria for discontinuing or modifying allocated interventions {11b}

When adverse events occur, the safety of participants should be put in the first place. According to the nature and severity of adverse events, different treatment methods such as termination of clinical trial, dose adjustment, symptomatic treatment, and observation can be adopted. In the event of withdrawal, investigators will communicate with the subject and complete the next scheduled visit content on the day of the participant's decision to withdraw. If a participant refuses further visits, the last available information before withdrawal will be used for safety and efficacy evaluations. Investigators should record the reasons for withdrawal in detail and document them in the case report form (CRF).

Withdrawal at investigator's discretion

An investigator may decide to withdraw a subject from the trial if it is deemed unsafe or inappropriate for the subject to continue. The following circumstances warrant withdrawal:

(1) Lack of symptom improvement, symptom exacerbation, or emergence of new severe symptoms (e.g., chest distress, palpitations).
(2) Allergic reactions or serious adverse events that, in the physician's judgment, necessitate trial discontinuation.

(3) Poor subject compliance (product compliance < 80% or > 120%), or self-initiated changes to medication or use of prohibited drugs (considered withdrawal at the time of change).
(4) Post-randomization discovery of serious violations of inclusion or exclusion criteria.
(5) Participants or their guardians unwilling or unable to continue the trial for any reason, requesting withdrawal.
(6) Participants not explicitly requesting withdrawal but becoming lost to follow-up by not accepting product use and testing.

Participant-initiated withdrawal

Participants have the right to withdraw from the trial at any time, as stipulated in the informed consent form. Withdrawal is also considered to have occurred if a participant ceases to accept product use and testing, even without explicit request to withdraw. Reasons for withdrawal should be explored and documented, such as perceived lack of efficacy, intolerability of adverse effects, inability to continue clinical research, financial concerns, or unexplained loss to follow-up.

Strategies to improve adherence to interventions {11c}

During the intervention, all participants will be asked to record their daily oil consumption, diet and exercise, and to have their photos taken with a dietitian. Daily reminders will be sent to each participant via instant message to inform them. In addition, all participants will be given written and oral instructions for each meal plan. Also, researchers will meet with them monthly to encourage them to stick to the eating plan.

Relevant concomitant care permitted or prohibited during the trial {11d}

Concurrent medications

(1) Participants with chronic conditions may continue long-term medications.
(2) Continue regular treatment, including antihypertensive medications.
(3) Symptomatic treatments will be decided by researchers and recorded.
(4) All concurrent medications must be detailed in the CRF.

Prohibited concurrent treatments

(1) Usage of unprescribed medications or methods for chronic metabolic syndrome and asymptomatic hyperuricemia will be prohibited.
(2) Usage of unmarketed drugs or other clinical trial medications will be also forbidden.

Provisions for post-trial care {30}

Unblinding will be performed at the end of the 12-week clinical study evaluation or when participants experience trial-related adverse events, including clinically significant laboratory abnormalities. After discussion by the research team, the participant will receive continued medical care at the sub-center where the respective clinical study is conducted.

Outcomes {12}

Primary and secondary outcomes

The primary outcomes will be the levels of serum uric acid during the intervention 4 weeks ± 3 days, 8 weeks ± 3 days, and 12 weeks ± 3 days. The secondary outcomes will be the levels of fasting blood glucose, 2 h postprandial blood glucose, total cholesterol, triglyceride, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, blood pressure, weight, body mass index, waist circumference, and average intima-media thickness of common carotid artery during the intervention 4 weeks ± 3 days, 8 weeks ± 3 days, and 12 weeks ± 3 days; fasting insulin, fasting C-peptide, 2 h postprandial C-peptide, glycosylated hemoglobin, and HOMA-IR during the intervention 12 weeks ± 3 days.

Participant timeline {13}

A time schedule of enrolment, interventions, and assessments is presented in Fig. 2.

Sample size {14}

In accordance with statistical principles, we utilized the PASS 2021 software's Tests for Two Means in a Repeated Measures Design to calculate the sample size. Parameters were set based on preliminary trial results and expert consultation as follows: statistical power $(1-\beta)=0.8$, significance level $(\alpha)=0.05$, the ratio of sample sizes between the two groups = 1:1, expected difference in uric acid means between groups = 55 μmol/L, which is based on our previous small sample trial of diacylglycerol edible oil intervention in patients with chronic metabolic syndrome, a single arm trial, and the difference in mean before and after analysis after 2 months of intervention (not published in any journal), number of time points = 3, type of covariance = compound symmetry, standard deviation of a single observed sample = 137.99 μmol/L (range: 6.18 ~ 137.99), correlation coefficient between different time points = 0.55 (range: 0.23 ~ 0.55). The calculation determined that 70 cases per group are required, with an additional 20% to account for loss to follow-up,

	STUDY PERIOD					
	Enrolment	Allocation	Post-allocation			Close-out
Timepoint[a]	$-t_1$	0	t_1	t_2	t_3	t_3
ENROLMENT:						
Eligibility screen	×					
Informed consent	×					
Baseline collection	×					
Allocation		×				
INTERVENTIONS:						
Intervention group			—	—	—	
Control group			—	—	—	
ASSESSMENTS:						
Patient characteristics	×					
Serum uric acid	×		×	×	×	
Fasting insulin, fasting c-peptide, 2 h postprandial c-peptide, glycosylated hemoglobin and HOMA-IR	×				×	
Fasting blood glucose and 2h postprandial blood glucose	×		×	×	×	
TC, TG, HDL-C and LDL-C[b]	×		×	×	×	
Blood pressure, weight, body mass index and waist circumference	×		×	×	×	
Average intima-media thickness of common carotid artery	×				×	
Serum metabolomics and intestinal metagenomics	×				×	
Adverse events			×	×	×	
Data analysis						×

Fig. 2 Schedule of enrolment, interventions, and assessments. [a]t_1, week 4 ± 3 days; t_2, week 8 ± 3 days; t_3, week 12 ± 3 days. [b]TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol

resulting in a final sample size of 88 cases per group. Consequently, the total sample size for this trial is 176 cases, with an equal ratio of intervention to control groups, i.e., 88 cases in each group.

Recruitment {15}

We will collect 176 participants from The Eighth Affiliated Hospital of Sun Yat-sen University, Shenzhen Hospital of Southern Medical University, The Third Affiliated Hospital of Guangzhou Medical University, and Shenzhen Hospital of Guangzhou University of Chinese Medicine. Recruitment posters containing inclusion and exclusion criteria will be posted in clinics and on the social networking platform. Interested participants will be invited to the hospitals for a physical examination and baseline assessment and will be informed that their participation is voluntary and that choosing not to participate will not affect their care.

Assignment of interventions: allocation

Sequence generation {16a}

The method of stratification and block randomization will be adopted, with the center as the stratification factor, and block randomization will be carried out in each center. A random sequence (random table) will be generated by statisticians who did not participate in this study and statistical analysis using SAS statistical software according to the stratification factor and group proportion, and the experimental group and the control group will be randomized at a ratio of 1:1. Each participant will be given a unique identifier.

Concealment mechanism {16b}

The allocation sequence will be sealed in an opaque file bag as a first-order blind base. Participants included in the study will receive the corresponding intervention according to the group number set out in the envelope.

Implementation {16c}

The randomized sequence will be generated by statisticians who are not involved in the trial study and statistical analysis using SAS statistical software, and the randomized sequence will be hidden from the investigators and patients participating in the clinical trial. The investigators will enroll and assign participants according to the generated unique identifier. Once the grouping of participants will be determined, it will not be allowed to change the grouping.

Assignment of interventions: blinding

Who will be blinded {17a}

This trial will be double-blinded, meaning that the participants, the investigator, data analysts, and all participating researchers will be unaware of the grouping, and each participants will be given a unique identification number. Assignments will be provided only to groups "A" and "B" without intervention or control to the data analysts, leaving the statisticians blind to the assignments for the interim and final analyses.

Procedure for unblinding if needed {17b}

Patients, investigators, statisticians, and all participants will be blinded throughout the study. The subgroup of participants will be not revealed until 12 weeks of the trial and after statistical analysis, or after adverse events had occurred in patients.

Data collection and management

Plans for assessment and collection of outcomes {18a}

Information on the results of the study including baseline data and the collection of study data will be recorded in the form of a spreadsheet. All researchers and staff will be trained to simulate data acquisition at least 3 times prior to clinical data acquisition. Researchers responsible for the collection or transport of blood or urine or feces will be trained in standard operating procedures. Researchers in the assessment of results will receive specific evaluation training to understand the definition of results to ensure the accuracy and standardization of the assessment.

Plans to promote participant retention and complete follow-up {18b}

Third-party health managers will oversee the study, providing dietary and exercise guidance as well as supervision. They will also remind participants to attend follow-up sessions, thereby enhancing participant retention and ensuring the completion of follow-up procedures. Also, we will arrange flexible time and place for participants to follow up. Patients' questions and concerns will be responded to in a timely manner. In addition, the dropout rate has been taken into account in our sample calculation.

Data management {19}

Strict data management and quality control procedures will be applied to ensure the accuracy and integrity of the data. Data management programs will be developed to address data outliers, thereby improving data quality. After the data manager completes the data review report, the data review meeting will be coordinated by the study sponsor or contract research organization. The data manager will report on the data management during the research process, and the study sponsor, the main researcher, the data manager, and the statistician will conduct the final review of the unresolved data issues, discuss the statistical plan, discuss the division of the data set together, check the records, etc. After all data questions and data set divisions have been agreed, and the data has been updated based on data review comments (if any), the data manager will notify the database designer to lock the database and hand over the clean database to the statisticians after obtaining written locking approval. After the database is locked, it is generally not easy to unlock the database. If incorrect data is found and the database needs to be unlocked after evaluation by all parties, the data administrator will submit a written unlock application, clearly describing the incorrect data to be changed, the reason for the change, and the date of the change. The unlock application will be jointly signed by the personnel of all parties who have signed the lock database. The database designer will be informed by the data administrator to unlock the database, after which all data revisions have an audit trace. Once the data has been revised, it will be locked again following the same process as when the database was first locked. Access to the data will be limited to the research team. Patient's personal information will be kept separately and not accessible to any third-party personnel other than authorized research team personnel.

Confidentiality {27}

All patient data and personal information will be kept strictly confidential and stored not only throughout the trial but also after the trial. Each participant will be given an identification code that will replace their identity on the CAF and other documents. The identity information of participants will also be strictly encrypted or hidden during data transmission.

Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in this trial/future use {33}

At week 0, 4, 8, and 12, with the consent of the participants, additional blood samples (1 × 3 ml EDTA tube, 1 × 3 ml heparin sodium anticoagulant tube, and 1 × 3 ml BD tube), urine samples (1 × 3 ml tube), and feces samples (≈100 mg) will be collected together for future genomic analysis and biomarker analysis. The blood will be centrifuged within 24 h of collection and then packaged and stored in a freezer at − 80 °C. Urine and feces samples will be placed in a freezer at − 20 °C immediately after collection and transferred to the − 80 °C freezer within 24 h. These samples will be stored in the human biological sample resource bank of the Eighth Affiliated Hospital of Sun Yat-sen University.

Statistical methods

Statistical methods for primary and secondary outcomes {20a}

The primary outcome will be covariance analysis. If the interaction between group and center is not statistically significant (judged at the test level of 0.1), the primary analysis model will include baseline serum uric acid value, center, and group. The least squares mean of each group, the difference between the least squares mean of each group, and the 95% confidence interval are obtained. If the lower limit of confidence interval is > 0, it can be considered that the uric acid lowering effect of experimental group is better than that of control group. For other analyses, the detection value of serum uric acid and the difference between each visiting site and baseline will be described. Two independent samples *t*-test will be used for comparison between groups, and paired *t*-test will be used for comparison between the results of each visiting site and baseline. Two independent samples *t*-test or Wilcoxon rank sum test will be used for inter-group comparison of secondary results, and paired *t*-test or Wilcoxon signed rank test will be used for intra-group comparison. Pearson chi-square test or Fisher exact test will be used for comparison between data sets. The Wilcoxon rank sum test will be used to compare rank groups. Data will be reported as mean ± SD. Bilateral tests will be used for all statistical inferences, and the test level with statistical significance will be set as 0.05. The confidence intervals for parameters will be estimated using bilateral 95% confidence intervals.

Interim analyses {21b}

No interim analysis is planned for this study.

Methods for additional analyses (e.g., subgroup analyses) {20b}

We do not plan to perform any statistical analysis beyond our expectations. All statistical analysis methods have been described in this text. If additional analysis is deemed necessary for the analysis of confounding factors, we will elaborate on its justification in future reports of our findings.

Methods in analysis to handle protocol non-adherence and any statistical methods to handle missing data {20c}

Researchers will regularly remind and encourage participants to adhere to the protocol by phone or through social media to reduce protocol non-adherence. Intention to treat (ITT) analysis method will be used to deal with the problem of protocol non-adherence. We will use the mixed model without any hoc imputation to handle missing data.

Plans to give access to the full protocol, participant-level data, and statistical code {31c}

The full protocol, participant-level data, and statistical codes of this study are available from the corresponding authors upon reasonable request.

Oversight and monitoring

Composition of the coordinating center and trial steering committee {5d}

The coordinating center of this study will be the Department of Traditional Chinese Medicine of the Eighth Affiliated Hospital of Sun Yat-sen University. The research assistant will communicate with the patient daily and schedule appointments as necessary. The project Steering Group for this trial will consist of all the authors listed and will be responsible for the overall oversight of the trial, including the formulation and revision of the protocol, progress of the trial, compliance with the agreed protocol, risks to participants, and consideration of new information affecting deviations from the trial protocol, publication of the study report, etc. They will maintain daily communication and contact through social networks.

Stakeholders in this trial are patients with chronic metabolic syndrome combined with asymptomatic hyperuricemia, families, and healthcare providers, whose comments and recommendations will be collected into the feasibility study. If their comments and recommendations contribute to the improvement of clinical trial design, they will be adopted and implemented. Therefore, if any modifications to the study appear to be necessary, they will be reported and

justified as modifications to the trial and in the final paper.

Composition of the data monitoring committee, its role and reporting structure {21a}

The data monitoring committee is composed of four authors (Gui-yu Li, Jia-jun Yu, Li Wang, Dan-ping Xu) and statisticians. They are responsible for monitoring the primary efficacy measures, secondary efficacy measures, and safety measures data related to the trial to ensure the correctness and completeness of the data. Statisticians are responsible for data entry and statistical analysis. We appoint a third-party data monitoring committee, independent of this trial, to monitor and review the effectiveness and safety of the trial participants, as well as data quality, protocol compliance, etc.

Adverse event reporting and harms {22}

Participants will be closely monitored with weekly phone or video calls for any potential adverse events related to this trial. Patients will be asked about their discomfort in a standardized manner and safety indicators associated with the trial will be closely monitored. In the event of an adverse event, immediate measures are taken to protect the safety of the subject. The details of adverse events will be recorded in the original medical record and CRF, and their persistence, prognosis, and disappearance will be recorded according to the circumstances. All adverse events associated with this trial will be reported to the investigators and sponsors.

Frequency and plans for auditing trial conduct {23}

The Project Management team will meet quarterly to review the implementation and progress of the trial to ensure continued compliance and data accuracy. In addition, depending on the specific phase of the trial or key milestones, we may schedule additional reviews to enhance oversight. For example, more intensive reviews may be conducted during the start-up phase of a trial or near completion. All reviews will be conducted by a third-party review team independent of the investigator and sponsor to ensure objectivity and impartiality.

Plans for communicating important protocol amendments to relevant parties (e.g., trial participants, ethical committees) {25}

When there is a major change in the research protocol, a report will be submitted to the Ethics Review Committee in a timely manner, and the corresponding information will be updated on the Chinese clinical trial registration platform. All key decisions should be made by the corresponding authors with full consideration of the opinions of the research team.

Dissemination plans {31a}

The findings will be published in a scientific journal. At the same time, in order to popularize scientific knowledge, we will prepare a public facing version of the abstract, which we plan to distribute to relevant patient support groups to facilitate the wide dissemination of information. In addition, these research results will also be displayed in the clinic to facilitate direct understanding and communication between patients and medical professionals.

Discussion

This protocol describes a multicenter randomized controlled trial to investigate whether DAG edible oil (containing > 80% DAG) improves chronic metabolic syndrome with asymptomatic hyperuricemia compared to conventional triacylglycerol oils. Chronic metabolic syndrome is a multifactor disease, characterized by central obesity, high blood pressure, high blood sugar, and abnormal blood lipid levels; these factors increase the risk of cardiovascular disease.

Hyperuricemia, as part of metabolic syndrome, is associated with inflammation, insulin resistance, and oxidative stress and may exacerbate the pathological processes of metabolic syndrome. However, although several studies have shown that DAG oil is effective in stimulating fat oxidation and resting metabolic rate [20], there are relatively few studies on the effect of DAG oil on chronic metabolic syndrome complicated with hyperuricemia, and its efficacy is not fully understood.

Because of its unique molecular structure, DAG oil is thought to have a positive effect on lipid metabolism and insulin sensitivity. This scheme proposes that dietary DAG oil intake, instead of triacylglycerol oil, may have a positive effect on the metabolic status of patients with chronic metabolic syndrome by improving the lipid profile and enhancing insulin sensitivity, and then may have a positive effect on hyperuricemia.

This study protocol designed a randomized controlled trial to evaluate the effects of DAG oil on metabolic syndrome patients with asymptomatic hyperuricemia. The study will evaluate the effects of DAG oil on serum uric acid levels, lipid profiles, insulin sensitivity, and other metabolic parameters. The findings will help determine whether DAG oil offers a new treatment strategy for metabolic syndrome patients.

In conclusion, this study scheme offers a promising field of study, namely DAG oil on chronic metabolic syndrome with the potential effect of asymptomatic hyperuricemia. The completion and clinically validated results of this study may provide new insights and treatment options for the management of metabolic syndrome patients.

Trial status

Protocol version 1.1, 28/12/2022.
Chinese Clinical Trial Registry identifier: ChiCTR2400085336.
Recruitment status: ongoing.
Trial registration date: June 5, 2024.
Date recruitment began: May 13, 2022.
Estimated primary completion date: May 2025.
Estimated study completion date: May 2025.

Abbreviations

ALT	Alanine aminotransferase
ASCVD	Atherosclerotic cardiovascular disease
AST	Aspartate aminotransferase
CRF	Case report form
CMS	Chronic metabolic syndrome
Cr	Serum creatinine
DAG	Diacylglycerol
HDL-C	High-density lipoprotein cholesterol
LDL-C	Low-density lipoprotein cholesterol
SUA	Serum uric acid
TAG	Triacylglycerol
TC	Total cholesterol
TG	Triglyceride

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Authors' contributions {31b}
XDP is the principal investigator. XDP and WYH conceived the study protocol and led the proposal and protocol development. XDP, LGY, ZCF, HZQ, PCL, YJJ, WL, ZQ, LYY, LY, ZXL, ZZT, HTH, LMS, LSZ, and ZNW will perform the research and contribute to the participant recruitment. LGY drafted the manuscript. ZCF, HZQ, and PCL revised the manuscript. LGY, ZCF, HZQ, PCL, YJJ, WL, ZQ, LYY, LY, ZXL, ZZT, HTH, LMS, LSZ, ZNW, and ZFYN collect the data. All authors read and approved the final manuscript.

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Data availability {29}
The data of this study are available from the corresponding authors (WYH and XDP) upon reasonable request.

Declarations

Ethics approval and consent to participate {24}
This study has been approved by the Ethics Committee of the Eighth Affiliated Hospital of Sun Yat-sen University (2022–099-02/03). All participants will be provided with a detailed explanation of the research protocol in both oral and written forms, with an opportunity to ask questions, before giving their written informed consent. The study findings will be disseminated through peer-reviewed publications and conference presentations.

Consent for publication {32}
Not applicable—no identifying images or other personal or clinical details of participants are presented here or will be presented in reports of the trial results. The participant information materials and informed consent form are available from the corresponding author on request.

Competing interests {28}
The authors declare that they have no competing interests.

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