Effect of date seed (*Phoenix dactylifera*) supplementation as functional food on cardiometabolic risk factors, metabolic endotoxaemia and mental health in patients with type 2 diabetes mellitus: a blinded randomised controlled trial protocol

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ABSTRACT

Introduction  Recently, the improvement of chronic hyperglycaemia-related damage of type 2 diabetes mellitus (T2DM) through functional food consumption has attracted the attention of many clinicians. This study aims to determine the effectiveness of date seed powder (DSP) as a functional food (prebiotic) on the cardiometabolic risk factors, oxidative stress, anti-/inflammatory biomarkers, metabolic endotoxaemia (gut microbiota), adipokines, hypothalamic–pituitary–adrenal axis biomarkers, immune system, anthropometric indices and mental health in patients with T2DM.

Methods  This study protocol will be conducted as randomised, triple-blind, placebo-controlled trial with the inclusion of 48 patients with T2DM. The participants will be randomly assigned into two equal groups of intervention (n=24) and placebo (n=24) and receive 5g/day of DSP or placebo for 8 weeks, respectively. At baseline and post-intervention, fasting blood samples will be collected to assess the serum levels of lipid profile, glycaemic indices, antioxidant and oxidative stress, anti-/inflammatory biomarkers, lipo polysaccharide, 8-hydroxy- guanine, adipokines, hypothalamic–pituitary–adrenal axis biomarkers, immune system and mental health. Data will be analysed using the SPSS software (V.16.0). To compare the quantitative variables, paired and unpaired Student’s t-tests and covariance analyses will be used.

Discussion  In this study, the potential effects of DSP on patients with T2DM will be evaluated for the first time. It is hoped that the results would increase the body of scientific knowledge about DSP supplementation on the cardiometabolic risk factors, oxidative stress, anti-/inflammatory biomarkers, metabolic endotoxaemia, adipokines, hypothalamic–pituitary–adrenal axis biomarkers, immune system, anthropometric indices and mental health in patients with T2DM.

Ethics and dissemination  The study protocol was approved by the Ethical Committee of the Tabriz University of Medical Sciences, Tabriz, Iran (code: IR.TBZMED.REC.1400.752).

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This will be the first triple-blind, placebo-controlled, randomised clinical trial to investigate the potential effects of date seed powder (DSP) supplementation on type 2 diabetes mellitus.
- DSP as a waste product can be considered as a functional food with multiple nutritional properties.
- Application of DSP as valuable by-products can minimise the cost of waste management.
- There will be two main limitations in this study: (a) using a fixed supplement dose and (b) not assessing the levels of polyphenols or flavonoid content.

INTRODUCTION

Diabetes mellitus (DM) has been identified as one of the most common and severe disorders in recent years, leading to many complications such as limiting life expectancy, threatening life, causing disability to patients, and imposing a heavy financial burden on patients and the health system.1 The International Diabetes Federation estimated that 536.6 million people developed diabetes in 2021, which will increase by up to 46% by 2045.2 According to the WHO, diabetes will be the seventh leading cause of mortality by 2050.3 In Iran, about 15.0% and 25.4% of adults aged 35–70 years are reported to have diabetes and pre-diabetes, respectively.4 Diabetes is closely linked with metabolic syndrome, obesity, insulin resistance, oxidative stress, hyperlipidaemia and proinflammatory status.5–8 Due to the detrimental...
consequences of diabetes, aetiological assessments should be regarded as a priority in healthcare systems.9

Besides genetic and environmental factors such as poor eating habits, physical inactivity, ageing and psychological disorders, chronic hyperglycaemia is another crucial risk factor. The impressive body of evidence has increasingly focused on chronic hyperglycaemia in the development of oxidative stress as a trigger of macrovascular and microvascular complications, including neuropathy, retinopathy, nephropathy and ulceration of type 2 DM (T2DM).10 11 Furthermore, dysbiosis of the gut microbiota has recently been identified as a critical factor in metabolic disorders associated with T2DM.12 According to evidence, there is a change in gut microflora among patients with T2DM towards gram-negative bacteria, and an increase in Firmicutes over Bacteroidetes is associated with an inflammatory cascade, increased insulin resistance and oxidative stress.13 The changed gut microbiota leads to the entrance of lipopolysaccharides (LPS) into the blood as the major compounds of outer membranes of gram-negative bacteria and develops metabolic endotoxaemia.14 Thus, it seems that improvement in the capability of antioxidant defence system, gut microbiota and inflammatory responses via adjunctive treatment may be a potential approach to combat the complications of T2DM. It has been hypothesised that functional food can modulate inflammation, oxidative stress and subsequently metabolic endotoxaemia by altering the gut microbiota, increasing the capacity and ability of the body’s antioxidant defence.15 16 So, functional food with multiple properties is probably more beneficial in controlling the complications of T2DM.17

Recently, the date seed, an inedible part of date fruit and the main waste in the industry of date processing, has attracted the attention of many researchers.18 Considering the high amounts of polyphenols (hesperidin, quercetin, kaempferol, etc), phenolic acid (allergic, epicatechin, catechol, chlorogenic, etc), carotenoids, total dietary fibre (such as pectin, β-glucan, arabinoxylan), fat, protein, minerals, and various other nutrients and functional elements in date seed, it has been considered as a functional food with multiple properties.19–23 The maximum tolerated level of date seeds was reported to be at a dose of 0.5 g/kg/day.24 However, administration of DSP and maltodextrin at the specified dosages (5 g/day; 2.5 g at breakfast and 2.5 g at dinner) will not have adverse events.24 However, the investigators will record all potential adverse events reported by the patients during each visit or follow-up. The participants will be consulted or treated if they experience an unexpected severe adverse effect free of charge. The main investigator will ensure that the corrective action improves the unfavourable impact if necessary. In addition, the Ethics Committee will be notified of any adverse effects.

**MATERIALS AND METHODS**

**Protocol amendments**

All authors will review and approve any protocol changes or adjustments. The main investigator will examine any protocol revisions or additions, and other investigators will support her. Finally, any changes will be reported.

**Safety assessments**

It is expected that administration of DSP and maltodextrin at the specified dosages (5 g/day; 2.5 g at breakfast and 2.5 g at dinner) will not have adverse events.24 However, the investigators will record all potential adverse events reported by the patients during each visit or follow-up. The participants will be consulted or treated if they experience an unexpected severe adverse effect free of charge. The main investigator will ensure that the corrective action improves the unfavourable impact if necessary. In addition, the Ethics Committee will be notified of any adverse effects.

**Study design and participants**

A randomised, triple-blind, placebo-controlled clinical trial will be conducted to evaluate the effects of DSP on cardiometabolic risk factors, oxidative stress, anti-inflammatory biomarkers, metabolic endotoxaemia, adipokines, hypothalamic–pituitary–adrenal axis biomarkers, immune system, anthropometric indices and mental health in patients with T2DM. The trial will be carried out in the Azfalipour Hospital and other clinics in Kerman, Iran. Also, we will use public platforms such as WhatsApp, posters, advertisements, telephone calls and medical staff introductions to recruitment of patients.

**Figure 1** shows an overview of this research.

In this article, we will use the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) to report the results and the details of the study protocol, including the timing of enrolment, interventions and assessments (online supplemental file 1, SPIRIT Checklist).30 Table 1 shows the diagram of the study protocol.

**Inclusion criteria**

In this randomised controlled trial, patients with T2DM with fasting plasma glucose (FPG) levels of ≥126 mg/dL21 will be recruited. Inclusion criteria will be as follows: at least 6 months of history of diabetes; age range of 30–50 years; body mass index (BMI) between 25 and 35; no insulin therapy; use of blood glucose-lowering medicines and propensity to take DSP during the study. Exclusion criteria will be as follows: the use of insulin therapy; using specific medications such as antidepressants,
amphetamines, oral steroids, etc; taking antioxidant supplements at least 3 months before recruitment; experiencing weight changes more than 5%–7% during 3 months; a history of a special and low-calorie diet during the last 6 months; the presence of other diseases or impairments such as disorders of the thyroid, heart, kidney, liver and lung; infectious problems and digestive problems; cancers; alcohol consumption or smoking; pregnancy; lactation; being an athlete; strenuous physical activity; unwillingness to consume DSP and gastrointestinal symptoms during the study. During the study, the participants will be asked to maintain their usual level of physical activity.

**Randomisation and blinding**

All eligible patients will be included in the study. After a 2-week run-in period, the qualified patients will be randomly assigned into two equal groups of placebo (n=24) and intervention (n=24) for 8 weeks at a 1:1 ratio using stratified randomisation based on age, gender and BMI. Then, we will use the random allocation software (V.1.0, Saghaei, Isfahan, Iran) to perform randomised blocks (sizes 2 and 4). During the run-in period, the patients will be asked to stabilise their diet according to diabetic recommendations for patients with T2DM, maintain their physical activity and refrain from taking any supplements to prepare for the trial. The subjects will be grouped by a third person to ensure the concealment of the research aspects. The main researcher, the people who collect the data, the statistical consultant and the people who are being studied will all remain blind regarding the groups of subjects until the end of the analysis.

**Figure 1** Consolidated Standards of Reporting Trials (CONSORT) diagram.

**Table 1** The Standard Protocol Items: Recommendations for Interventional Trials chart for the study process

<table>
<thead>
<tr>
<th>Time point</th>
<th>Enrolment</th>
<th>Allocation</th>
<th>Intervention</th>
<th>Close-out</th>
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<td>−t1</td>
<td>X</td>
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**Enrolment**

- Eligibility screen: X
- Informed consent: X X
- Questionnaires: X
- 3-day food diary: X X
- Anthropometrics: X
- Blood taking: X X
- Allocation: X

**Interventions**

- Date seed group: X X
- Placebo group: X X

**Assessments**

- Dietary status: X
- Blood pressure: X
- Questionnaires: X
- Biochemical assessments: X
- Safety: X

The ‘X’ indicates what is done in the given period. t0, allocation; −t1, 2-week pre-allocation; t1, at the beginning of the study; t2, at 8 weeks; t3, end of study.
Intervention

The patients will receive either 5g/day (2.5g at breakfast and 2.5g at dinner) of DSP supplement (date seed, Flavinea Co, Iran) or maltodextrin as a placebo (Jiujiang Huirong Trade Co, China) with a glass of water or with semisolid food like yoghurt for 8weeks, respectively. We will help patients to understand how to incorporate the supplement into their regular diet. DSP and maltodextrin powders are odourless and flavourless. Both powders will be provided in identical opaque packages. The powders will be delivered to participants at baseline and 8 weeks after the study. Participants will be contacted twice a week to ensure compliance, keep up with physical activity and resolve supplement administration issues. A checklist will also be provided to all participants to assess their compliance. Also, we will count the packages to determine adherence to the regular consumption of powders. Participants who do not take more than 10% of the packages will be excluded from the study. After completing the study, the results will be sent to participants via email and details will be included in a research newsletter suitable for non-specialist audience.

Sample size

Since there are no clinical trials evaluating the effects of DSP on patients with T2DM, we determined the sample size according to the change in high-density lipoprotein (HDL) levels, which was the primary outcome of the study by Jubayer et al in individuals with hyperlipidaemia. Considering the mean difference of 6.2mg/dL between the two groups, the sample size was calculated to be at least 22 subjects for each group, with a power of 80% and 95% confidence levels by the Power Analysis and Sample Size software (V.15, NCSS, Kaysville, Utah, USA). The sample size will be increased to 24 subjects for each group, considering a 10% dropout rate throughout the trial.

Primary and secondary outcomes

The primary outcomes of the current study include: fasting blood glucose (FBG), glycosylated haemoglobin (HbA1c), fructosamine, insulin, lipid profile (total cholesterol (TC), HDLs, low-density lipoproteins (LDLs), triglycerides (TGs)), high-sensitivity C reactive protein (hs-CRP), tumour necrosis factor-α (TNF-α), interleukin-6 (IL-6), interleukin-4 (IL-4), interleukin-18 (IL-18), interleukin-10 (IL-10), LPS, total antioxidant capacity (TAC), malondialdehyde (MDA), Oxidative Stress Index (OSI), total oxidant status (TOS), superoxide dismutase (SOD), glutathione peroxidase (GSH-Px), catalase (CAT), soluble receptor for AGEs (sRAGE), carboxymethyl (hs-) triglycerides (TGs), high-sensitivity C reactive protein (hs-CRP), tumour necrosis factor-α (TNF-α), interleukin-6 (IL-6), interleukin-4 (IL-4), interleukin-18 (IL-18), interleukin-10 (IL-10), LPS, total antioxidant capacity (TAC), malondialdehyde (MDA), Oxidative Stress Index (OSI), total oxidant status (TOS), superoxide dismutase (SOD), glutathione peroxidase (GSH-Px), catalase (CAT), soluble receptor for AGEs (sRAGE), carboxymethyl lysine (CML), pentosidine, 8-iso-prostaglandin F2α (8-iso-PGF2α), uric acid, protein carbonyl and nitric oxide (NO). Meanwhile, the secondary outcomes include anthropometric indices, blood pressure, dietary intake, cortisol, brain-derived neurotrophic factor (BDNF), tryptophan (TRP), adrenocorticotropic hormone (ACTH), kynurenine (KYN), cluster reference 4 (CD4), cluster reference 8 (CD8) and mental health. The variables, including energy intake, weight changes, the baseline of glycaemic indices, lipid profile, LPS, inflammatory markers, mental health and oxidative stress biomarkers, will be used as covariate variables.

Clinical and paraclinical assessment

We will explain the study to the participants at the baseline. All subjects will complete demographic, physical activity level (PAL) and mental health questionnaires, and report any current use of medications. Participants’ PAL will be assessed before and after the intervention using the International Physical Activity Questionnaire (IPAQ) Short-Form. Mental health data will be collected by using the Depression, Anxiety, and Stress Scale (DASS) and a General Health Questionnaire (GHQ). Fourteen items in the DASS questionnaire are divided into three subscales to measure depression, anxiety and stress. Additionally, the 28-item GHQ will assess five other subscales: somatic symptoms, anxiety, insomnia, social dysfunction and severe depression. Before taking supplements and at the end of the intervention, dietary intake will be evaluated using a 3-day food diary (2days for weekdays and 1day for the weekend). Food record data will be evaluated through ‘Nutritionist 4’ software (First Databank, Hearst Corp, San Bruno, California, USA).

Assessments of anthropometric indices will be done at baseline and post-study. Measurements of weight will be done without shoes and with minimal clothing to the nearest 0.1kg using a reliable digital scale (Seca, Hamburg, Germany). The height of the participants will be measured barefoot using a metre mounted on the wall with a precision of 0.1 cm. An inelastic tape will be placed between the lowest rib and the upper iliac crest to measure the waist circumference. The hip circumference will be measured by holding the tape parallel to the ground and measuring around the widest part of the buttocks without pressing the skin. Neck circumference will be measured perpendicular to the axis of the neck below the laryngeal prominence, and a minimum circumference will be calculated to the nearest 0.1 cm. The BMI will be calculated by dividing the weight (kg) by the square of the height (m²). The same person will measure all anthropometric measurements to minimise measurement errors. After a resting time of 30 min, blood pressure will be measured three times by a DinaMap Compact, and the mean will be reported.

Before and at the end of the trial, 10mL of blood will be collected from patients following a fasting period of 10–12 hours. To separate the serum from whole blood, centrifugation will be used. Biochemical parameters, such as glycaemic parameters, lipid profile, hs-CRP and uric acid, will be immediately measured after collecting the samples. The rest of the serum will be stored at ~70°C until the end of the intervention. The FPG, TG, TC, HDL-cholesterol, uric acid and hs-CRP concentrations will be determined using the enzymatic colorimetric assay method. The LDL-cholesterol will be obtained using...
using the HPLC-Darniographic method will be used to determine HbA1c.

Determined through a chemiluminescent immunoassay dual-system. Plasma insulin levels will be determined through a chemiluminescent immunoassay method. For measuring GSH-Px, SOD and TAC, colorimetric methods will be applied. MDA levels will be determined with thiobarbituric acid, as a thiobarbituric acid reactive substance, using a spectrofluorometer. CAT activity will be measured using the method described by Aebi. The OSI, Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) and Quantitative Insulin Sensitivity Check Index (QUICKI) will be calculated using the following formula: OSI = 100 × (TOS/TAC), \[ \text{HOMA-IR} = \frac{\text{fasting insulin} \times \text{FBG}}{\text{mU/mL} \times \text{mM/L}} \times 22.5 \]
\[ \text{QUICKI} = \frac{1}{\log \left( \text{fasting insulin} \times \text{mU/mL} + \log (\text{FBG}, \text{mg/dL}) \right)} \]

Data management
We will collect data related to demographics, mental health, physical activity, food intake, anthropometric indices, blood pressure and biochemical parameters. Also, the related questionnaires, including IPAQ, DASS, GHQ and a 3-day food diary will be used to collect data by a trained expert. The intention-to-treat principle will be used to analyse the data of patients excluded from the trial for any reason. All participants will be followed up for 8 weeks.

Confidentiality
All the data will be kept in password-protected file cabinets with restricted access. A code identification number will be used to identify data collection and forms to preserve participant confidentiality. All records, including names and other information that can be used to identify a person, will remain separate from study data and will be coded with a distinctive code number.

Statistical analysis
SPSS (SPSS for Windows, V.16.0) will be used to analyse the data. For quantitative and qualitative variables, results will be presented in terms of mean±SD and frequency (per cent), respectively. Kolmogorov-Smirnov will be used to determine if the variables are normally distributed. To assess baseline differences between groups qualitatively and quantitatively, the X² test and the unpaired Student’s t-test will be used, respectively. Log transformation will be done for non-normal data. An analysis of covariance will be conducted to compare quantitative variables between groups post-intervention. Also, we will use the paired t-test to determine within-group differences. For determining the difference between groups, the per cent change will be calculated as follows: 100×(intervention values-placebo values)/placebo values. The significance level for all tests will be considered less than 0.05.

Patient and public involvement
It will not be necessary to involve patients in designing, conducting, reporting or disseminating the findings of the research.

DISCUSSION
In the proposed clinical trial, we will evaluate the effects of DSP as a functional food on the cardiometabolic risk factors, oxidative stress, anti-/inflammatory biomarkers, blood pressure, metabolic endotoxaemia, adipokines, hypothalamic–pituitary–adrenal axis biomarkers, immune system, anthropometric indices and mental health in patients with T2DM.

A growing body of evidence indicates that functional food supplementation has a significant effect on macrovascular and microvascular complications of T2DM. Recently, researchers, nutritionists and clinicians have focused on functional foods as multinutrient supplements. Since functional food supplement ingredients contain various chemical properties, they have multiple concurrent effects, such as modulation of glycaemic indices, improvement of antioxidant capacity, lipid profile, inflammation, gut microbiota and ultimately enhanced quality of life in patients with T2DM. It has been shown that date seeds, as a rich source of polyphenol and prebiotic fibre, have a wide range of healthy properties, including antioxidant, anti-inflammatory, antitumour, hepatoprotective, nephroprotective, antihyperlipidaemic, antiaging and memory improvement. Polyphenols, flavan-3-ols and prebiotics play an essential role in the mentioned activities. In several studies, date seeds regulated oxidative stress, inflammation, immunity and lipid profile by acting as a powerful source of antioxidants and prebiotics. An animal study examining the effect of date seeds on nephrotoxicity, aroused by CCH4, reported that date seeds had a protective function and could improve the histology of the kidneys via increasing SOD and glutathione S-transferase levels and decreasing MDA, GSH and NO levels. A clinical trial on postmenopausal women reported that supplementation with 2.5 g/day of date seed for 2 weeks significantly decreased MDA levels and increased SOD and GSH-Px activities. Isworo et al revealed that consuming 2.5 g of date seed for 14 days decreased the expression of interleukin-1β, transforming growth factor β, cyclo-oxygenase-1 and cyclo-oxygenase-2 in middle-aged women. A clinical trial on patients with hyperlipidaemia found that supplementing with date seed (600 mg/day for 90 days) improved TC, TG, LDL and HDL levels. Date seed supplementation may improve metabolic responses, oxidative stress status, anti-/inflammatory biomarkers and mental health via scavenging free radicals, inhibiting lipid peroxidation, suppression of nuclear factor-kB, reduction of...
NO production, modulating mitogen-activated protein kinases and nuclear factor erythroid-related factor 2. Furthermore, the prebiotic properties of date seeds may decrease metabolic endotoxaemia by shifting gut microbiota toward beneficial bacteria, such as Lactobacillus and Bifidobacterium and reducing pathogenic bacteria such as Clostridium. This is the first study to evaluate the effects of DSP consumption on the cardiometabolic risk factors, oxidative stress, anti-/inflammatory biomarkers, blood pressure, 8-OH-G, metabolic endotoxaemia, adipokines, hypothalamic–pituitary–adrenal axis biomarkers, immune system, anthropometric indices and mental health in patients with T2DM. It has hypothesised that DSP supplementation can improve metabolic parameters, dysbiosis gut microbiota, inflammation, oxidative stress, immunity and mental health in individuals with T2DM.

CONCLUSION

We expect that DSP consumption as a functional food will improve metabolic parameters, oxidative stress, inflammation, metabolic endotoxaemia and mental health in patients with T2DM. The results of this trial can be used to provide evidence-based recommendations for clinicians, nutritionists and patients with T2DM.

TRIAL STATUS

This is the first version of the present protocol (dated 25 May 2022). Recruiting participants is underway.

ETHICS AND DISSEMINATION

The study will be conducted based on the protocol and the ethical principles initiated in the Declaration of Helsinki. Informed consent will be obtained from participants at the baseline visit after all participants have been fully informed about the study’s purpose, methods, potential risks and rights. The Ethical Committee of Tabriz University of Medical Sciences, Tabriz, Iran approved the study protocol (code: IR.TBZMED.REC.1400.752), and it was registered on the Iranian Registry of Clinical Trials website (www.irct.ir/IRCT20150205020965N10). The results of this trial will be published in a refereed journal and shared both online and in print.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

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