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Effect of HEAT therapy in patiEnts with type 2 Diabetes mellitus (HEATED): protocol for a randomised controlled trial

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ABSTRACT

Introduction The burden of type 2 diabetes mellitus (T2DM) is increasing worldwide. Heat therapy has been found effective in improving glycaemic control. However, to date, there is a lack of randomised controlled studies investigating the efficacy of heat therapy in T2DM. Therefore, we aim to investigate whether heat therapy with natural thermal mineral water can improve glycaemic control in patients with T2DM.

Methods and analysis The HEAT therapy in patiEnts with type 2 Diabetes mellitus (HEATED) Study is a single-centre, two-arm randomised controlled trial being conducted at Harkány Thermal Rehabilitation Centre in Hungary. Patients with T2DM will be randomly assigned to group A (bath sessions in 38°C natural thermal mineral water) and group B (baths in thermoneutral water (30°C–32°C)). Both groups will complete a maximum of 5 weekly visits, averaging 50–60 visits over the 12-week study. Each session will last 30 min, with a physical check-up before the bath. At baseline, patients' T2DM status will be investigated thoroughly. Possible microvascular and macrovascular complications of T2DM will be assessed with physical and laboratory examinations. The short form-36 questionnaire will assess the quality of life. Patients will also be evaluated at weeks 4, 8 and 12. The primary endpoint will be the change of glycated haemoglobin from baseline to week 12. An estimated 65 patients will be enrolled per group, with a sample size re-estimation at the enrolment of 50% of the calculated sample size.

Ethics and dissemination The study has been approved by the Scientific and Research Ethics Committee of the Hungarian Medical Research Council (818-2/2022/EÜIG). Written informed consent is required from all participants. We will disseminate our results to the medical community and will publish our results in peer-reviewed journals.

Trial registration number ClinicalTrials.gov, NCT05237219.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This is a two-armed, randomised controlled study, which can provide high-level evidence on the efficacy of heat therapy in type 2 diabetes mellitus (T2DM).
⇒ There will be thorough examination of the patients' T2DM at baseline and after the end of the 12-week intervention.
⇒ Blinding the participants is impossible due to the water temperatures in the intervention and control groups.
⇒ The intervention will be performed in one centre, which will delay the study's completion.
⇒ An important limitation is the lack of a planned postintervention follow-up.

INTRODUCTION

The incidence and prevalence of type 2 diabetes mellitus (T2DM) and associated diseases are increasing, becoming a major global health problem.[1] T2DM is characterised by hyperglycaemic resulting from insulin resistance and progressive impairment of insulin secretion. It is associated with obesity, low-grade inflammation and a high risk for cardiovascular diseases.[1 2]

Lifestyle interventions such as dietary modification, enhancement of physical activity, and weight loss can prevent the development of T2DM, play an essential role in managing glycaemic control in T2DM patients, and reduce cardiovascular risk factors.[3] Exercise has a beneficial effect by promoting insulin sensitivity, glycaemic control, lipid profile, immune function, lowering blood pressure, and decreasing cardiovascular and overall mortality risks.[4]

It has been suggested that repeated passive heat exposure with hot tub therapy, sauna or hot spa water immersion induces adaptive mechanisms similar to exercise and might have a beneficial effect on insulin resistance, glycaemic control and cardiometabolic health.[5–8]

According to primary rodent models, the critical elements in these adaptive mechanisms are heat shock proteins (HSPs), stimulated by the rise of body temperature due to exercise or passive heating.[9–11]

HSPs are highly conserved proteins acting as molecular chaperons; their expression is upregulated by stressful insults like heat, cold, hypoxia or oxidative stress. They guard cells and cellular elements via regulation of protein folding and degradation, inhibit apoptosis, protect against oxidative stress and inflammation, increase resistance to further stress, and have a role in cell signalling and regulation of metabolism.[12] Altered cellular localisation and expression profile of HSPs are linked to T2DM, where low intracellular (iHSP) and high extracellular levels are detected. Since diabetes is a disease characterised by protein glycation, low-grade inflammation, and oxidative stress, low iHSP contributes to impaired stress response, promoting the proinflammatory state that changes insulin signalling and reduces insulin sensitivity. Induction of HSPs or restoration of HSP levels either by exercise or passive heating attenuates the harmful effects of subclinical inflammation, increases insulin sensitivity and improves glycaemic control.[13] Membrane alterations affect signalling pathways from membrane lipids to HSP genes and play fundamental roles in the aetiology of type 2 diabetes. On the other hand, the plasma membrane lipid composition's dietary modulation may improve T2DM by lowering serum glucose levels.[14]

Hooper first investigated heat therapy's effects in T2DM patients in 1999.[15] He found a significant decrease in mean fasting plasma glucose and glycated haemoglobin (HbA1c) levels and improvements in body weight in eight T2DM individuals after taking a daily hot tub bath for 3 weeks. Since that report, a handful of studies investigated chronic passive heating on glycaemic control in T2DM patients. Some studies focused on obese individuals with a relatively small subgroup of T2DM patients.[16 17]

Ely *et al*[18] investigated heat therapy in women with polycystic ovary syndrome, commonly associated with obesity and insulin resistance. They found improvements in whole-body glucose uptake, insulin sensitivity and insulin signalling after 30 times 1-hour hot tub sessions for 8–10 weeks. In another study, they also experienced beneficial changes in cardiovascular risk profile.[19]

Further studies have also reported positive effects of chronic heating (hot water immersion or heat chamber therapy) in fasting insulin, serum glucose concentration and blood pressure in overweight individuals.[7 20]

A mild abdominal electrical stimulation with heat shock was investigated in obese type 2 diabetic patients in a prospective randomised trial by Kondo.[21] They found significantly improved visceral adiposity, glycaemic control, insulin resistance, systemic inflammation, renal function, hepatic steatosis and lipid profile after use.

To date, no randomised control trial has investigated the effect of chronic whole-body passive heating (heat therapy) on glycaemic control, focusing on T2DM patients.

Objectives

This study aims to determine the effects of regular whole-body passive heating on cardiovascular and cardiometabolic health in type 2 diabetic patients. We hypothesise that regular passive heating via hot water immersion will improve these patients' glycaemic and cardiovascular states. Our second goal is to investigate the potential mechanisms underlying the beneficial action of heating. These findings might demonstrate that heat therapy could be an alternative or supplemental intervention to improve the metabolic and cardiovascular state in type 2 diabetes.

METHODS AND ANALYSIS

Study design and intervention

The study is a prospective, randomised, two-arm controlled clinical trial. The patient recruitment will be performed at the 2nd Department of Internal Medicine and Nephrological, Diabetological Center (University of Pécs, Medical School) and in Harkány Thermal Rehabilitation Centre in Hungary. We will enrol eligible adult patients with T2DM who consent to participate in this study. They will be randomised into two groups. The interventional group (A) will undergo repeated whole-body passive heating in 38°C natural thermal mineral water. Participants in the control group (B) are going to dip in thermoneutral natural thermal mineral water (30°C–32°C) bath following the same process as in the

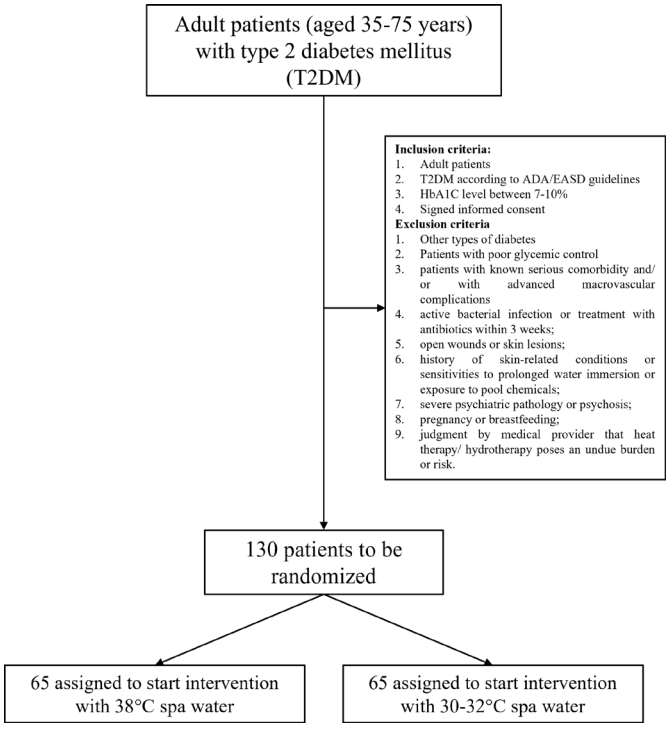

Figure 1 Trial flowchart. ADA, American Diabetes Association; EASD, European Association for the Study of Diabetes; HbA1C, glycated haemoglobin; T2DM, type 2 diabetes mellitus.

	ENROLLMENT	ALLOCATION	INTERVENTION				CLOSE-OUT
TIMEPOINT	Within 3 weeks	Day 0	Day 1	Week 4	Week 8	Week 12	Final visit < 48 h after the last inertvention
ENROLLMENT:							
Eligibility screen	X						
Informed consent	X						
Allocation		X					
INTERVENTIONS:							
Intervention with 38°C spa water			←	—	—	→	
Control with 30-32°C spa water			←	—	—	→	
Assessment of adverse events			←	—	—	→	
ASSESSMENTS:							
Questionnaire A		X					
Questionnaire B				X	X	X	

Figure 2 Schedule of enrolment, interventions and assessments.

interventional group (figure 1). During the intervention, the patients will be asked to continue their daily routine.

Participants' baseline data (medical history, current treatment, anthropometric data) will be recorded after informed consent and randomisation (figure 2). We will perform a baseline routine laboratory examination after a 12-hour fasting and functional analyses. Laboratory assessments will be repeated on weeks 4 and 8 and close-out. The final follow-up will be carried out after the last intervention on week 12.

Trial organisation, committee and boards

This trial's guarantor is the Institute for Translation Medicine, Medical School, University of Pécs, Pécs, Hungary. To date, the institute has started several high-quality clinical trials in the field of gastroenterology, intensive care medicine and COVID-19.[22]

The steering committee (SC) will be led by PH (gastroenterologist, internal medicine specialist) and LV (basic research specialist). The members will be ZE (internal medicine specialist, nephrologist), JS (internal medicine specialist, nephrologist), NN (balneotherapy specialist), BE (multidisciplinary unit specialist), SV (clinical research specialist), IW (diabetologist, nephrologist, internal medicine specialist), NF (biostatistical specialist). SC will make the relevant decisions during the study according to participation and dropouts.

The international advisory board (ITAB) will include PH and PG, who will provide independent external advice and guidance on strategic matters. In addition, board members provided important professional advice.

The independent data management board (IDMB) will ensure proper data handling.

Study protocol development

The SC and ITAB members designed the study protocol following the Standard Protocol Items: Recommendations for Interventional Trials 2013 Statement (online supplemental file 1).[23]

We performed a systematic review and meta-analysis to evaluate the already published trials on this topic. The results of which were used in the planning of this trial.[24]

Patient and public involvement

Three patients who would have been eligible for the study with T2DM were invited to the study protocol development. All were provided detailed information on the study, including the complete protocol. In addition, they advised the following: (1) all of them understood the protocol and expressed that they would participate in the study, (2) highlighted the importance of proper organisation of the daily visits to Harkány, (3) in this respect, they would consider the duration of the intervention feasible and (4) they would agree on the performed examinations and the number of biological sample collection. We have revised and modified the original protocol accordingly.

Study population

All eligible patients with T2DM[25] from the outpatient care of the 2nd Department of Internal Medicine and Nephrological, Diabetological Center (University of Pécs, Medical School) or patients under rheumatological treatment in Harkány Thermal Rehabilitation Centre will be informed about the possibility to take part in the trial. After the physician delineates the study design and intervention, patients should confirm their intention to participate by signing the written informed consent.

The inclusion criteria will be: (1) male and female patients between 35 and 75 years; (2) patients with type 2 diabetes diagnosed according to the American Diabetes Association and the European Association for the Study of Diabetes guidelines[25]; (3) serum HbA1c level between 7% and 10% (53–86 mmol/mol); (4) signed written informed consent form (online supplemental file 2).

The exclusion criteria will be: (1) other type of diabetes mellitus; (2) patients with poor glycaemic control or unstable diabetes[26]; (3) patients with known serious comorbidity and/or with advanced macrovascular complications in particular: cardiovascular (acute coronary diseases and/or transient ischaemic attack, stroke (in the last 6 months), severe heart failure (New York Heart Association (NYHA) III–IV), severe cardiac arrhythmia, malignancy diagnosed within 5 years (except successfully treated non-melanoma skin cancer), liver cirrhosis (Child-Pugh B and C), end-stage renal disease (estimated glomerular filtration rate (eGFR)<15 mL/min), uncontrolled endocrine, gastrointestinal, rheumatological, pulmonary etc, diseases, patients with epilepsy; (4) active bacterial infection or treatment with antibiotics within 3 weeks; (5) open wounds or skin lesions; (6) history of skin-related conditions or sensitivity to prolonged water immersion or exposure to pool chemicals; (7) severe psychiatric pathology or psychosis; (8) pregnancy or breastfeeding; (9) judgement by medical provider that heat therapy/ hydrotherapy poses an undue burden or risk; (10) participating in other ongoing clinical trials; (11) heat or balneotherapy in the past 3 months; (12)

morbid obesity (body mass index>40 kg/m^2); (13) steroid treatment; (14) active autoimmune diseases; (15) COVID-19 in the past 3 months.

Baseline assessments

Eligible participants' baseline evaluation will be performed at the 2nd Department of Internal Medicine and Nephrological, Diabetological Center.

A medical history will be recorded, and a physical examination and evaluation of the current status will be performed. The patients' T2DM status will be investigated thoroughly. Possible microvascular and macrovascular complications will be evaluated. We will use the Diabetic Neuropathy Symptom Score, measurement of current perception threshold (performed with neurometer),[27] and 128 Hz tuning fork to assess peripheral neuropathy. A Neuropad will be used for the measurement of autonomic neuropathy.[28] Furthermore, blood pressure evaluation and electrocardiography will be performed. We will also perform arterial stiffness measurement through carotid–femoral pulse wave velocity measurement. After enrolment, an obstructive sleep apnea assessment and 24-hour blood pressure monitoring will be carried out. Meanwhile, overnight pulse oximetry will determine a patient's cardiopulmonary status.

Laboratory analyses will be performed at the Department of Laboratory Medicine (University of Pécs, Medical School). First, a blood sample for routine blood examination will be taken after an overnight fasting period. The measured parameters will be the following: complete blood count, fasting plasma glucose, sodium (Na2+), potassium (K+), blood urea nitrogen, creatinine, eGFR, total protein, serum albumin, bilirubin, alanine aminotransferase, aspartate aminotransferase, alkaline phosphate, lactate dehydrogenase, gamma-glutamyl transferase (GGT), total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), triglyceride, HbA1c, fasting plasma insulin, high-sensitivity C reactive protein, coagulation panel, iron, transferrin, transferrin saturation, ferritin, uric acid, interleukin 6.

Similarly, urine analysis will be carried out for the following parameters: urine routine test, albumin, glucose and ketones. Furthermore, albumin/creatinine, protein/creatinine ratio and fractional excretion of amino acids will be measured.

At the 2nd Department of Internal Medicine and Nephrological, Diabetological Center's Laboratory, the following will be measured: orthotyrosine, metatyrosine and paratyrosine levels to determine the degree of oxidative stress.

LipidArt, Szeged, Hungary, will carry out these measurements using a previously published methodology. High-sensitivity shotgun mass spectrometry will be used to characterise the lipidome of plasma and polymorphonuclear blood cells.[29 30] The HSP and insulin signalling-related gene expression will be determined from polymorphonuclear cells.[31]

Health-related quality of life (QoL) will be assessed using the health survey short form-36.[32]

QoL assessment and the enlisted examinations mentioned above will be repeated in the same way within 48 hours after the last bath session. Laboratory parameter measurements will be performed at baseline on weeks 4, 8 and 12.

Randomisation

Eligible patients will be randomised to the two intervention groups after signing the written informed consent. The participants' allocation to the different groups will be based on predefined randomisation lists generated by a computer programme. The IDMB will prepare the distribution sequence with a block size of four and an allocation ratio of 1:1.

Blinding

Due to the interventions' characteristics (warm and thermoneutral water), blinding participants is not feasible. Physicians and outcome assessors remain blinded, except for the healthcare personnel providing the interventions. Trial statisticians will be blinded to treatment groups during data analyses.

Interventions

The interventions will be performed at Harkány Thermal Rehabilitation Centre. Participants can wear their regular swimsuits for the interventions. We will use pure natural thermal mineral water without any herbs or medicines. See characteristics of the natural thermal mineral water below.

Both the intervention and control groups will receive 60 sessions of whole-body baths. We will use 38°C natural thermal mineral water in the intervention group. Thermoneutral natural thermal mineral water (30°C–32°C) will be used in the controls. Each session will last 30 min. The sessions will be performed once daily for 12 consecutive weeks, except on the weekends. Each session begins 1–2 hours after a light meal. Participants will be asked to refrain from physical exertion during the immersion. Baseline parameters will be reassessed in both groups on the day after the last session.

The rationale for using 38°C water is a probable heating effect on body temperature. Based on an internal analysis of the Harkány Thermal Rehabilitation Centre, using natural thermal mineral water of 38°C will elevate patients' core temperature by an average of 1°C. We will monitor the patients' core temperature with an infrared forehead thermometer. According to prior testing, this body temperature measurement method is suitable for in situ adjustments of the patients' immersion temperature to achieve a body temperature increase of at least 1°C.

Before and during each intervention, a physician will supervise the patients for safety issues. In addition, before each intervention, a standard physical examination (arterial blood pressure, heart rate and finger-stick glucose monitoring) will be performed. In T2DM patients with

insulin therapy, the daily insulin requirement will be calculated based on glucose monitoring.

During the study period, the participants will be asked to continue their daily activities without any new weight reduction procedure or change in their diet. We will also ask them to continue their usual treatment for T2DM and other comorbidities.

Composition of mineral water of Harkány

Harkány is a city located in the Southern Transdanubia region in Hungary. The medical water rich in sulfur was discovered 150 years ago. Since then, the number of tourists visiting the spa of Harkány has reached one million people yearly. The average temperature of the natural thermal mineral water when reaching the surface is 62.5°C, which can be tempered to 38°C and 30°C–32°C used in our study. The water temperature will be continuously monitored. Mineral content of the water is about 1000 mg/L, with the following composition: sodium 150 mg/L, ammonium 1.53 mg/L, calcium 51 mg/L, magnesium 15 mg/L, iron 0.05 mg/L, potassium 12.0 mg/L, total cations: 230.1 mg/L, chloride 110 mg/L, bromide 0.32 mg/L, iodide 0.07 mg/L, fluoride 1.19 mg/L, bicarbonate 565 mg/L, sulfide 12.1 mg/L, total phosphate 0.16 mg/L, total anions: 689 mg/L, metaboric acid 6.6 mg/L, silicic acid 54 mg/L, free sulfuric acid 170 mg/L (see https://harkanyfurdo.hu/en/spa/thermal).

Endpoints

Primary outcome

The primary efficacy endpoint will be the absolute change of HbA1c level between baseline and 12 weeks. It will be compared between the interventional and control groups. On the other hand, the primary safety endpoint will be the intervention-related adverse events. We will assess adverse events from enrolment to the final visit.

Secondary outcomes

The following secondary endpoints will be examined: (1) absolute change in HbA1c level at 4 and 8 weeks compared with baseline; (2) change in fasting plasma glucose; (3) change in fasting insulin and Homeostatic Model Assessment for Insulin Resistance in patients treated with oral antidiabetic drugs; (4) decrease of daily insulin dose in subjects treated with insulin; (5) change in body mass index; (6) changes in cardiovascular parameters (blood pressure, pulse, arterial stiffness); (7) potential detectable change in measurable microvascular complications of T2DM (eg, albuminuria, or measurement of neuropathy); (8) fasting liver enzymes (alkaline phosphatase, alanine transaminase, aspartate transaminase, GGT), the lipid panel (ie, total cholesterol, LDL cholesterol and HDL cholesterol, triglycerides); (9) changes in renal function (GFR, creatinine level), (10) modification of thrombocyte aggregation; (11) changes in markers of (micro)inflammation; (12) alteration of HSP expression and insulin signalling in polymorphonuclear cells; (13) analysis of the lipidom of plasma and polymorphonuclear cells; (14) change in obstructive sleep apnea, overnight pulse oximetry and 24-hour blood pressure monitoring.

We will assess each secondary outcome from baseline to 4, 8 and 12 weeks.

Data collection and management

Data collection will be continuous during the study, and we will use predefined questionnaires (see figure 2 and online supplemental files 3 and 4). Paper-based documentation containing personal data can only be accessed by those directly involved in the research. After data collection, patients' data will be stored electronically and anonymously using electronic case report forms (eCRF). The IDMB will handle the data. The investigators will ensure that the data in the eCRF are accurate, complete and legible. Data from completed eCRFs will be validated in four steps. Missing data will be referred to the investigators.

Biological sample collection

For collecting biological samples, signed informed consent is required from every patient. During routine laboratory measurement, additional blood samples (serum and plasma samples) will be collected at the time of the enrolment and after 4, 8 and 12 weeks. The biobank of the Institute for Translational Medicine will be used to store samples. The samples will be stored in a −80°C freezer and marked with a personal identification number given at the study entry. The blood samples can be used for the analysis of additional laboratory parameters later if they are required.

Safety and adverse events

Participants will be under continuous medical control during and at least 30 min after the intervention to prevent adverse events. The following mild and moderate adverse events can appear: (1) allergic reaction to mineral water, (2) dry and itchy skin, (3) weakness or fatigue due to hot water, (4) skin burn can appear, however with continuous monitoring of the thermal water this can be prevented. On the other hand, a sudden decrease in systolic blood pressure can occur because warm water can deteriorate cardiac baroreceptor sensitivity.[33] We note that a hypotensive syncope causing sudden death by drowning was reported as a severe adverse event in a previous study.[34]

All the participants will be asked to leave the bath if they feel it is too hot. When feeling dizzy after leaving the tub, participants will be asked to stay seated until they can walk safely again. At the end of each session, we will measure participants' blood pressure and pulse rate.

In case of any adverse change in the participant's status or occurrence of serious adverse events, the intervention should be stopped immediately, and the cause of the symptom must be evaluated and treated.

Physicians will report the adverse event on a separate form, which must be sent to the SC. The SC will discuss it, and if it is confirmed as a real adverse event, it will be

presented to the relevant institutional and national ethics committee (http://www.ett.hu/tukeb.htm).

Withdrawal from the study

IDMB, participants and investigators can submit a request for dropout from the perprotocol analysis. SC will discuss every filed case and decide not to include the participant in the per-protocol analysis based on the available information. Drop out of the study subjects from per-protocol analysis occurs if: (1) any disturbing factor appears that makes the participant unable to continue the intervention, (2) if the number of completed interventions is less than 80% of the planned total (missed interventions or the duration of the intervention is less than 20 min), (3) serious adverse event occurs that prevents the participant from continuing the intervention, (4) sudden death.

Sample size and interim analysis

The IDMB and the biostatistical specialist calculated the sample size before starting the trial. Based on the systematic literature search, we have chosen the eligible trial articles dealing with heat therapy in patients with T2DM as a reference. Olah *et al*,[16] in a randomised trial on 20 patients with T2DM, found a mean HbA1c change of 1.1% (SD 0.61) in the intervention group and 0.98% (SD 0.52) in the control group after a 3-week follow-up period. On the other hand, based on the study of Hirst *et al*,[35] 12 weeks after the intervention, we can assume a 2.54 times higher change in the HbA1c level in both groups.

Based on this set-up with a dropout rate of 20%, 80% power, and 95% significance level, we calculated a sample size of 65 for both groups. An interim analysis will be performed at 50% of the estimated sample size for the primary outcome. For the reassessment of the intervention duration, the analysis for the primary outcome will be carried out for the 4-week and 8-week HbA1c changes.

A safety analysis will be performed at 10% of the required sample size.

Statistical analysis

For endpoints, the intention-to-treat analysis will be the primary choice. A perprotocol analysis will be carried out for the primary and secondary endpoints. Baseline patient and disease characteristics will be analysed using descriptive analysis. Continuous variables will be described by mean, median, SD, ranges and categorical by absolute and relative frequencies. χ^2 tests will be applied to compare proportions between the different groups. Mean changes with SD for baseline to end-of-study visit and between interventional groups will also be presented. Descriptive statistics and individual listings of adverse events will also be shown for safety data.

The following subgroups will be made during the statistical analysis: (1) gender, (2) ages (<45 years, 45–60 years, 60–75 years), (3) body mass index (<20, 20–24.9, 25–29.9, 30–35, >35), (4) duration of the T2DM and (5) T2DM treatment.

Statistical analysis will be performed using SAS V.9.2 or SPSS V.19 (or later) statistical packages.

Trial duration

The trial's planned starting date is 1 September 2022 and the end date is 31 August 2023.

Additional information and plans

We will store blood samples from all participants for future laboratory analyses and build up a biobank for later clinical trials and basic science research. Participant consent is required for the collected samples. Also, long-term follow-up of enrolled participants is possible. The durability of heat therapy requires further studies.

ETHICS AND DISSEMINATION

The study has been approved by the Scientific and Research Ethics Committee of the Hungarian Medical Research Council (818-2/2022/EÜIG). Written informed consent is required from all participants. The study will be performed based on the Declaration of Helsinki and the principles of International Committee on Harmonization of Good Clinical Practice (ICH-GCP) guidelines. We will disseminate our results to the medical community and will publish our results in peer-reviewed journals.

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Contributors All authors were involved in the study design, edited, read and approved the final manuscript. PH and LV conceptualised the study. FD, JS and ZE performed the systematic literature search. JS, ZE, SV and BE designed the study and wrote the manuscript. NN and IP provided important background on the intervention. LV, ZT, ZB, MP, IP, PG and GB wrote the basic research part of the protocol. NF performed the sample size calculation and will manage the safety and interim analysis. PH and PG are members of the international advisory board. The head of the steering committee will be PH. The members will be ZE, JS, IW, NN, BE, SV, LV and NF.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods and analysis section for further details.

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